(Response) FDA does not dispute this, but following the FACT standards is voluntary, and evidence does not show that 100 percent of entities in the stem cell sector are currently following these standards. FDA believes that mandatory requirements are necessary to adequately protect public health and safety.

(Comment 186) One comment suggested that the requirement for oversight and audits would impose costs that might significantly reduce the number of participants in the National Marrow Donor Program.

(Response) We disagree. With respect to provisions governing oversight and audits, the agency notes the following. Section 1271.160(c) is expected to impose no new financial burden on affected entities. Section 1271.160(d) is expected to impose an additional burden of $228 on entities currently following FACT standards, and $1,140 in additional costs on firms not following these standards. Thus, the maximum burden on any one firm of these provisions is $1,140 per year. The agency does not view this as a significant cost burden, nor do we believe that these provisions will significantly reduce the number of donor centers participating in the National Marrow Donor Program.

(Comment 187) One comment expressed serious concerns and reservations regarding the accuracy of FDA's estimates of the

risks associated with hematopoietic stem/progenitor cell transplants, and the costs and benefits of the proposed rule. Two comments argued that the costs for a bone marrow transplant are much different in 2001 than they were in 1994, and that much of the cost is for supportive care and not due to contamination of the graft. Therefore, the benefits of the rule are overstated.

(Response) FDA has revised the analysis of impacts for stem cell facilities to reflect the most recent available risk and cost information. The agency points out that the cost for a bone marrow transplant was presented in the analysis of impacts of the proposed rule for illustrative purposes only, and was not used directly in generating an estimate of the benefits of the CGTP rule for stem cell facilities.

(Comment 188) One comment suggested that the impact of the software validation requirements on small tissue facilities would be beyond the means of many and could force them out of business. The comment suggested that § 1271.160(e) be amended to require software validation only if it is relied upon as the sole source of data for quality-related decisionmaking.

(Response) With respect to computer software validation FDA assumed: (1) None of the affected entities currently validate custom software, (2) 10 percent of all facilities in each sector have developed custom software requiring validation, and (3)

validation of custom software will require 60 hours of laboratory supervisor time ($36 per hour, total cost = $2,160 per affected entity). We have modified § 1271.160(e) to indicate that either validation or verification can be performed, whichever is appropriate. Verification is less burdensome.

(Comment 189) One comment suggested that annual human heart valve allograft distribution is likely ten-fold lower (5,000-6,000) than the 61,000 annually referenced in the preamble and, further, that fewer than 10 infections per year are caused by contaminated valves since direct reports by implanting surgeons suggests less than 1 per year.

(Response) FDA has revised the analysis of impacts of the CGTP final rule to reflect both information provided in the comment and information on the risks associated with human heart valve allograft reported in the clinical literature.

(Comment 190) One comment expressed concern that the CGTP rule will be particularly onerous on small business, and would like FDA to ensure that they are not creating artificial market barriers by implementing the rule.

(Response) Nearly all facilities in the HCT/P industry are recognized as small entities and most would be similarly affected by the rule. Further, the requirements of the CGTP final rule are largely met, and in some cases exceeded, by the

voluntary standards firms are required to meet to gain accreditation by professional associations in their respective HCT/P industry sectors. Finally, the agency's analysis suggests that the cost burden of the CGTP rule will not be significant (expressed as a percentage of average annual firm revenues) and, therefore, should not constitute a market barrier to small business.

(Comment 191) One comment noted that FDA chose not to certify that the rule would not have a significant economic impact on a substantial number of small entities. The comment suggested that FDA should increase its outreach to small entities in an effort to obtain the information necessary to fully assess the rule's impacts before finalization.

(Response) FDA's analysis of economic impacts is based on: Information obtained under the registration final rule; administrative data on the number of facilities within each industry sector; and the number of entities accredited by various industry associations. FDA also obtained information from individual experts identified through contact with the various industry professional associations. We explicitly recognized the uncertainty of our estimates with respect to the number of facilities in each sector, degree of compliance with current industry standards and impact of the rule on affected entities. In the proposed rule, FDA requested detailed industry

comment regarding our analysis of impacts, and data sources and underlying assumptions. Finally, the agency made presentations at the annual conferences of several industry professional associations, and held individual meetings with many of these groups at their request. We believe this represents a significant level of outreach and information gathering effort.

(Comment 192) One comment suggested that, upon publication of the final rule, FDA should address all comments received regarding small business impacts and provide an assessment of small business revenues that are likely to be affected.

(Response) FDA has provided responses to all comments received in the preamble to the final rule. A comprehensive assessment of the rule's effects on small business entities is provided in the analysis of economic impacts as required under the Regulatory Flexibility Act.

(Comment 193) One comment noted that if FDA significantly underestimated firm revenues, the rule's resultant costs to firms could be far greater than those estimated.

(Response) FDA believes that if average firm revenues were significantly underestimated, then the rule's resultant costs would appear greater (as a percentage of revenues) than they really are, thereby overstating the impact of the rule. We believe the comment intended to address the effect of FDA having overestimated firm revenues. In this case, compliance costs

(expressed as a percentage of revenues) would appear smaller than they really are, thereby understating the impact of the rule.

Nevertheless, FDA's estimates of average annual revenues were obtained from a variety of sources including a published study of the tissue banking industry, information obtained from industry consultants and other published data sources. In the CGTP proposed rule, FDA requested detailed industry comment on the distribution of firm revenues in the HCT/P industry, and also on our estimates of average revenue per firm. We received no detailed information in response to our request, and no comments provided alternative estimates of annual firm revenues.

(Comment 194) One comment suggested that § 1271.155 of the rule seems to allow all businesses affected by the regulation to seek an exemption or alternative from the requirements of the rule.

(Response) While an exemption from or an alternative to a particular provision of the rule may be requested by any business, the granting of such a request is by no means assured. The entity requesting an exemption or alternative must demonstrate that the exemption is justified based on scientific data and other evidence, and that the alternative satisfies the purpose of the requirement. Section 1271.155 does not provide a

mechanism by which all businesses may become generally exempt from compliance with the CGTP rule.

(Comment 195) One comment assumes that § 1271.155 is FDA's attempt to comply with section 603(c) of the Regulatory Flexibility Act, which requires agencies to identify any significant alternatives available to small entities in their initial regulatory flexibility analysis.

(Response) This assumption is incorrect. The agency has written the CGTP rule broadly so as to allow comprehensive regulatory oversight of the diverse HCT/P industry. Section 1271.155 is designed to provide some flexibility, recognizing that an exemption from, or alternative to, a specific provision may be appropriate given the unique properties of a particular HCT/P.

(Comment 196) One comment noted that the FDA estimates between 75 percent and 100 percent of affected entities are already compliant with the provisions of the CGTP rule, and questions whether the rule will create another layer of unnecessary recordkeeping and training requirements for the affected firms.

(Response) Because compliance with current voluntary industry standards is less that 100%, FDA believes the CGTP rule is the best way to establish a consistent standard of safety for marginal firms not currently following voluntary industry

standards and guidelines, and to protect public health and safety. We believe that the recordkeeping and training requirements are necessary to achieve the desired public health and safety goals.

(Comment 197) One comment expressed concern that the ultimate responsibility is placed in the hands of the firm distributing the HCT/P, while other firms will also be involved in manufacturing. Noting that the distributor is responsible for maintaining documentation from all other companies involved in manufacturing the HCT/P, the comment expressed concern that this will place an unacceptable burden on small entities, and suggests that, to minimize this burden, FDA should adopt an alternative approach, discussed in the proposed rule, using a cascading set of responsibilities.

(Response) Before Comment 28, we set out a table to assist establishments in understanding their responsibilities when multiple establishment are involved in manufacturing an HCT/P. At Comments 28 through 35 we discuss the allocation of responsibilities in § 1271.150(c) and 1271.265. FDA believes that this approach is largely consistent with the cascading set of responsibilities described in the comment and discussed at Comment 31. Both approaches place responsibility on each establishment that performs manufacturing functions, with the establishment that makes the product available for distribution

ultimately responsible for ensuring that the manufacturing and tracking records for an HCT/P demonstrate that it has been manufactured and tracked in compliance with the requirements of this subpart and subpart D.

IV. Effective Date of 21 CFR Part 1271 and Applicability of 21 CFR Part 1270

A. Effective Date for Part 1271

This final rule is effective May 25, 2005. All HCT/Ps recovered on or after the effective date must be in compliance with applicable requirements in part 1271.

As of the effective date, establishments that manufacture HCT/Ps defined in § 1271.3(d) that are regulated solely under the authority of section 361 of the PHS Act (as described in § 1271.10) must comply with all applicable requirements in part 1271, whether or not the HCT/P enters into interstate commerce.

The regulations under 21 CFR 207.20(f) and 807.20(d) require establishments that manufacture HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act to register and list their HCT/Ps following the procedures in subpart B of part 1271. Section 1271.21 requires HCT/P establishments to register and list every HCT/P that the establishment manufactures within 5 days after beginning operations, or within 30 days of the

effective date of the registration regulation, whichever is later. HCT/P establishments that manufacture HCT/Ps subject to investigational new drug (IND) or investigational device exemption (IDE) provisions are not required to register and list their HCT/Ps until the investigational HCT/P is approved through a Biologics License Application (BLA), a New Drug Application (NDA), or a Premarket Approval Application (PMA); or cleared through a Premarket Notification Submission (510(k)).

As required by §§ 210.1(c), 211.1(b), and 820.1(a), establishments that manufacture HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act also must comply with the requirements in subparts C and D of part 1271 in addition to all other applicable regulations.

B. Applicability of Part 1270

The retrospective application of part 1271 to human tissue, defined in § 1270.3(j), recovered before the effective date of the final rule would be overly burdensome and impractical. Therefore, we are not concurrently revoking part 1270 with the effective date of part 1271 as stated in the proposed rule (66 FR 1508 at 1524). However, we intend to revoke part 1270 in the future when we are confident that there is no human tissue regulated under 1270 available for use.

Part 1270 applies now only to human tissue defined in § 1270.3(j) and recovered before May 25, 2005. We have amended § 1270.3(j) to implement this provision. Products that meet the definition of HCT/P in § 1271.3(d) that are recovered before May 25, 2005, and that have been regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act will continue to be subject to the applicable requirements for drugs, devices, and/or biological products.

V. Analysis of Economic Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the principles identified in Executive Order 12866. The Office of Management and Budget (OMB) has determined that this final rule is a significant regulatory action as defined by the Executive order and so is subject to review.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The majority of establishments within the HCT/P industry that will be affected by this final rule can be classified as small business entities, and a number of these establishments will incur new costs. Because of the limited information with which to characterize the current good tissue practice at many of these establishments, and thus the increased effort required to meet the standards of the final rule, the cost impact on small business entities is uncertain. Therefore, the following analysis, along with other relevant sections of this preamble, represents FDA's final regulatory flexibility analysis.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing

> * * any rule that includes any Federal mandate that may result in the expenditure by State, local and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.

The current threshold after adjustment for inflation is $ 110 million. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

Based on the following economic analysis, FDA estimates that the total one-time costs to comply with this final rule will be approximately $6.91 million, and that the total annual or recurring costs will be about $7.13 million. These figures imply a total annualized cost estimate for the CGTP final rule of approximately $7.94 million to $8.11 million. The average annualized cost of CGTPs per affected small entity, expressed as a percentage of average annual revenue, ranges from 0.6 percent to 3 percent. This range of small entity impacts reflects uncertainty with respect to the current practices of affected entities and differences in the impact of the CGTP final rule across the various sectors of the HCT/P industry.

A. Risks Associated with HCT/Ps

FDA has conducted an extensive search for information with which to quantitatively assess and characterize the risks associated with HCT/Ps, but has found very little information available. The primary reason for this lack of information is the absence of mandatory reporting requirements for adverse events, including the incidence of communicable disease transmission and graft failure, associated with HCT/Ps. The

CGTP final rule will help to improve upon this situation by requiring entities that make HCT/Ps available for distribution to report to the agency any adverse reaction that meets the requirements of § 1271.350(a), as well as reports of HCT/P deviations required in § 1271.350(b). This information will be highly valuable to the agency in identifying and addressing areas of existing and emerging public health and safety risks associated with HCT/Ps. The available information regarding the risks associated with HCT/Ps known to the agency is summarized in the discussion that follows. Specific examples of risks associated with individual HCT/Ps are discussed in detail in section C of this analysis of economic impacts.

The HCT/P industry is currently growing and evolving rapidly. Since the CGTP proposed rule was published in January 2001, there have been significant increases in both the number of tissue donors and manufacturing establishments, as well as the number of HCT/Ps processed, distributed, and transplanted. Estimates of the current number of establishments in each sector of the HCT/P industry are presented in table 1b, along with recent information reflecting the approximate numbers of tissue donors and tissue products produced annually.

TABLE 1b.--NUMBERS OF HCT/P ESTABLISHMENTS, TISSUE DONORS AND PRODUCTS PRODUCED BY MAJOR INDUSTRY SECTOR

Type of HCT/P	Number of Establishments[1]	Number of Donors	Number of Products Produced Annually
Eye Tissue[2]	134	47,796	94,186

Conventional Tissue[3]	166	20,000	750,000
Hematopoietic Stem/Progenitor Cells[4]	425	5,700	6,031
Reproductive Tissue[5]	510	4,640	122,200

[1] Information obtained under the registration and listing final rule or provided by HCT/P industry professional associations. See section B.1 and table 3 of this analysis of economic impacts for additional details.
[2] EBAA, 1999.
[3] AATB, 1999.
[4] AABB/FACT, 1999.
[5] The American Society of Reproductive Medicine (ASRM), 1999.

One source of potential communicable disease transmission risk associated with HCT/Ps is a lack of standard quality assurance procedures and recordkeeping requirements intended to ensure compliance with such procedures. Currently, in every major sector of the HCT/P industry, professional organizations have in place standards specifying appropriate operating procedures that establishments should follow to ensure that the products produced are safe for use and of high quality. Individual establishments in the various sectors of the HCT/P industry may also apply for accreditation through these professional organizations, which periodically inspect member establishments to ensure that they are following the appropriate standards. However, as discussed in detail in V.B and C of this economic analysis, following industry standards and seeking accreditation through the professional organizations is voluntary, and the rates of compliance and accreditation within the various sectors of the HCT/P industry vary significantly. Furthermore, there are currently no comprehensive monitoring or enforcement mechanisms governing establishments that choose not

to follow voluntary industry standards or seek accreditation, and that may produce and distribute for use HCT/Ps that may present a serious threat to public health and safety.

The agency is aware of numerous reports of adverse health events and several patient deaths that have been linked to HCT/Ps. Transplantation of tissue has resulted in transmission of viral, bacterial, fungal, and other diseases, although such instances are rare. Some of these adverse events have been associated with HCT/Ps produced by large entities that do not follow voluntary industry standards and are not accredited by their respective professional associations. In March of 2002, the CDC published the results of their investigation of 26 reported cases of tissue allograft-associated infection, one of which resulted in the death of the patient (Ref.1). The CDC concluded that of the 26 reported cases, "14 (were) associated with a single tissue processor," and further suggested that their

> * * * findings * * * have important implications for patient safety and indicate that current federal regulations and industry standards on processing and quality control methods need to be enhanced and implemented to prevent * * * allograft-associated infections.

Problems due to inadequate product processing and quality controls, contributing to post-operative infection and/or graft failure, are one category of the many potential causes of the reported adverse health events associated with HCT/Ps. Implementation of the CGTP final rule, by establishing an enforceable set of product quality assurance procedures and standards, is expected to reduce the risk of communicable disease transmission as well as the incidence of other types of adverse health events associated with HCT/Ps.

Recent information on the number of infections following surgery, incidence of communicable disease transmission, graft failures, and additional surgeries required as a result for various types of HCT/Ps is summarized in table 2 of this document. Although these numbers suggest that the risks associated with the various types of HCT/Ps are relatively low, it is important to consider the limitations of these data.

It is highly unlikely that the available data provide an accurate accounting of the true risks associated with HCT/Ps because there is currently no mandatory reporting requirement for adverse health events, including communicable disease transmission and graft failure, associated with tissues. Thus, the case reports that are known to the agency are almost certainly not representative of the risks associated with HCT/Ps, because a significant number of these events may go

unreported. In the eye banking industry, the EBAA requests that adverse event information be voluntarily reported, but acknowledges that not all members provide this information. The AATB does not request information on the number of adverse events reported to accredited conventional tissue banks. Further, the New York Department of Health indicated that they know of no entity that collects information on graft failures or repeat surgeries due to complications associated with musculo-skeletal tissues. Thus, despite a significant effort on the part of the agency, very little information with which to identify and quantify the risks associated with various types of HCT/Ps was found. In summary, the limited information presented in this analysis of impacts is not likely representative of the true risks associated with HCT/Ps, because no mandatory adverse event reporting requirements exist, the information that is available is reported voluntarily and, in some sectors of the tissue industry, the necessary information is not available because it is not collected by any source.

TABLE 2.--SUMMARY OF AVAILABLE HCT/P RISK INFORMATION[1]

Type of HCT/P	Number of Transplants	Number of Infections	Number of Graft Failures	Additional Surgeries Required
Ocular (Eye)[2]	33,035	9	37	37
Musculo-Skeletal[4]	NDF[3]	52	NDF	4
Heart Valve Allografts[5]	4,000	26	41	41
Hematopoeitic Stem/Progenitor Cells; Peripheral Blood[6]	18,123 (in 1997)	NDF	NDF	NDF
Hematopoeitic Stem/Progenitor Cells; Cord Blood[7]	2000 (from 1988 to 2002, inclusive)	NDF	NDF	NDF

TABLE 2.--SUMMARY OF AVAILABLE HCT/P RISK INFORMATION[1]

Type of HCT/P	Number of Transplants	Number of Infections	Number of Graft Failures	Additional Surgeries Required

[1] Annual data except as noted otherwise.
[2] EBAA, 2001 Statistical Report.
[3] NDF: Denotes No Data Found or Available.
[4] AATB, 2001.
[5] FDA, CDRH, Office of Surveillance and Biometrics, 2001.
[6] Transfusion, Vol. 42, 2002.
[7] Current Opinion in Oncology, Vol. 14, No. 2, March 2002.

The agency obtained additional information on the risks associated with HCT/Ps by reviewing establishment inspection reports (EIRs) filed by agency inspectors. The following information summarizes some of the inspector's observations made in the course of their inspections of establishments processing human tissues. This information was obtained from a manual search of approximately 150 EIR reports filed in 2000 and 2001, and reflects observations from 15 of the 150 EIRs that were not citable under 21 CFR part 1271, but would be citable under 21 CFR part 1271. As such, this discussion is not a comprehensive assessment of the results of FDA inspections of HCT/P processing establishments. Instead, it is intended to provide an illustration of the type of processing and quality assurance problems that currently exist in the tissue industry, and that would be addressed through implementation of the CGTP final rule.

Failure to validate procedures for various stages of HCT/P processing was identified in 8 of the 15 reports. More

specifically, observations included failure to validate procedures for the prevention of infectious disease contamination and cross-contamination during processing, and failure to prepare written procedures for designating and identifying quarantined tissue. Failure to document the destruction or disposition of human tissue, failure to designate and identify the person responsible for making the determination that an HCT/P was suitable for transplantation, and/or failure to accompany quarantined tissue with records indicating the tissue was not determined to be suitable for transplantation were identified in 5 of the 15 reports. Failure to maintain adequate records of each significant step in the processing of human tissues and/or performance of infectious disease screening, as well as failure to maintain accurate records thereof, were cited in 6 of the 15 inspection reports. Finally, failure to prepare and follow written procedures for all significant steps for obtaining, reviewing, and assessing the relevant medical records of tissue donors, or failure to provide along with dispensed tissue a summary of the records of the donor eligibility determination, were cited in 7 of the 15 inspection reports. Although this summary of examples of FDA inspector's observations related to provisions under part 1270 is not comprehensive, it does indicate the type of procedures and quality control problems observed in HCT/P processing

establishments in 2000 and 2001. Each example could have an adverse impact on the HCT/P, and all are further addressed by various provisions of the CGTP final rule.

To gain additional insights into the risks associated with HCT/Ps, FDA also reviewed reports of adverse events associated with human tissue products submitted through the MedWatch system. Between 2000 and 2001, FDA received 21 voluntary MedWatch reports of problems associated with HCT/Ps. Because there is no mandatory requirement for reporting adverse reactions involving tissue products, the extent to which these reported events are representative of the risks associated with HCT/Ps during this period is unclear. It is likely, however, that a significant number of adverse events associated with HCT/Ps are unreported under the current voluntary MedWatch system. The 21 reported adverse events included: 4 patient deaths (3 of which were probably due to underlying disease and not directly attributable to HCT/Ps); 5 life-threatening situations; 5 surgical or other medical interventions; 2 cases of permanent disability; 9 additional hospitalizations; and 7 cases of mold contamination of HCT/P packaging material. Many of the potential underlying causes of these voluntarily reported adverse events are addressed by various provisions of the CGTP final rule, implementation of which is expected to reduce

communicable disease transmission risks and the number of adverse events associated with the various types of HCT/Ps.

B. Estimated Cost Impact

With the CGTP final rule, FDA is furthering completion of the set of proposals that represent a comprehensive new system for regulating the rapidly evolving HCT/P industry. Manufacturers of HCT/Ps may need to make certain changes to their operations to comply with this rule, such as creating new procedures revising existing procedures, and providing additional documentation. This final rule, in its entirety, affects several types of entities involved in the manufacture of HCT/Ps including eye banks, conventional tissue banks and establishments processing hematopoietic stem/progenitor cells. As explained elsewhere in this preamble, Assisted Reproductive Technology (ART) establishments and semen banks are subject only to the inspection and enforcement provisions of the CGTP final rule as they apply to donor eligibility requirements under subpart C. As such, reproductive tissue establishments will be only minimally affected by this final rule.

Information obtained under the registration final rule forms the basis for FDA's estimates of the number of affected eye banks and conventional tissue banks. The agency's estimates

of the number of affected eye banks, hematopoietic stem/progenitor cell establishments, ART establishments, and semen banks rely heavily on information obtained from various professional organizations associated with the HCT/P industry. Where good statistical data are not available, FDA's cost impact estimates have incorporated the quantitative judgments of individual experts identified through contacts with HCT/P industry professional associations. Because of the lack of comprehensive data with which to characterize patterns of current practice within each affected industry sector, and the importance of this data for development of an accurate assessment of cost impact, FDA requested detailed industry comment on the number of establishments involved in the manufacture of HCT/Ps, and the net change in quality assurance efforts needed for those establishments to comply with the CGTP proposed rule. To the extent possible, this information has been incorporated into FDA's analysis of the economic impact of this final rule.

1. The Number and Type of Entities Affected

The analysis of the economic impact of this final rule is organized around four major subgroups: Eye banks, conventional tissue banks, hematopoietic stem/progenitor cell establishments, and reproductive tissue establishments. The number of establishments and the percentage of establishments that follow

current industry standards are summarized in table 3 of this document. In estimating net new costs for eye banks, conventional tissue banks and hematopoietic stem/progenitor cell establishments, it is critical to account for establishment compliance with existing industry standards. In a number of these HCT/P sectors, current industry standards for many manufacturing operations meet or exceed the specifications in this final rule. Establishments following those standards will experience very little impact in complying with the new FDA standards.

As presented in table 3 of this document, FDA has a record of 134 registered establishments listing eye tissue including 96 eye banks, approximately 93 of which are currently accredited by the EBAA. According to industry experts, virtually all operating eye banks currently comply with EBAA medical and procedural standards for quality control. For affected eye banks, the incremental costs associated with this final rule result from additional quality assurance steps and process documentation as specified under the CGTP final rule.

FDA has a record of 166 registered tissue banks involved in the manufacture of other conventional HCT/Ps, e.g., skin allografts, bone allografts, fascia, tendons and ligaments (hereafter referred to as "conventional tissue banks"). The AATB lists approximately 75 accredited tissue banks and projects

another 40 to 60 members unaccredited. Industry sources report that approximately 75 to 80 percent of these establishments currently follow the voluntary standards established by the AATB. For these establishments, there will be some additional cost associated with review of this final rule and with alignment of their current SOPs with FDA's new requirements. There may also be some additional recurring cost, where documentation and quality control required under the CGTP final rule extend beyond current practice. For the remaining 20 to 25 percent of establishments not following the AATB standards, the cost of compliance will be somewhat higher. These establishments may need to establish more formal procedures and quality control measures, and may need to devote additional staff hours to performing these procedures and processing controls.

Establishments that produce hematopoietic stem/progenitor cells from peripheral blood or from umbilical cord blood will also be affected by this final rule. FDA finds that available data with which to estimate the number of peripheral blood stem/progenitor cell (PBSC) establishments and evaluate current practices are quite limited, and the actual number of PBSC establishments may range from 200 to 400. As of April 2002, CBER has a record of 178 voluntarily registered establishments listing "stem cell" as a type of product or establishment. The

National Marrow Donor Program (NMDP), which includes establishments that recover PBSCs, lists approximately 92 donor centers and 113 collection centers. Approximately 150 establishments involved with PBSCs are currently accredited by the AABB and an estimated 107 are accredited by the Foundation for the Accreditation of Cellular Therapy (FACT). Industry sources estimate that 80 of these establishments are seeking dual AABB/FACT accreditation, suggesting an unduplicated count of approximately 200 PBSC establishments assumed to be accredited by AABB and/or FACT. However, the number and manufacturing practices of nonaccredited establishments are unknown. The International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR) estimates that the total number of peripheral blood or bone marrow establishments may be as high as 400 (e.g., 200 more than the number estimated to be accredited by AABB and/or FACT), but the number of IBMTR/ABMTR-estimated establishments that actually process peripheral blood (as opposed to bone marrow) is uncertain. For the purposes of this analysis, FDA has assumed that 400 PBSC establishments will be affected by this final rule.

Although there is no single national organization that keeps track of the number of establishments for umbilical cord blood banking, FDA estimates that there are approximately 25

cord blood banks currently operating in the United States. These establishments would also seek accreditation through FACT or AABB. Based on this information, the agency estimates that a total of 425 establishments involved in manufacturing hematopoietic stem/progenitor cells would be affected by this final rule.

In addition, 67 establishments produce licensed biological products or approved medical devices that are currently regulated under the act and/or section 351 of the PHS Act, but would be subject to the provisions of this final rule. The impact of CGTPs on these firms is expected to be minimal because they are already subject to existing CGMP regulations for drugs or QS regulations for medical devices. Those requirements are largely consistent with the requirements of this final rule.

Finally, the inspection and enforcement provisions of this final rule, as they apply to donor eligibility requirements under subpart C, will affect establishments involved with reproductive tissue, primarily ART establishments and semen banks. For purposes of this discussion, references to ART establishments include infertility clinics, as well as andrology and embryology laboratories. The ASRM has a membership of approximately 400 fertility centers, 370 of which have provided reports for the 1999 Society for Assisted Reproductive Technology registry (Ref. 29). The ASRM also has a 1996 list of

approximately 110 semen banks operating in the United States. Based on conversations with consultants, most ART and commercial semen banking establishments currently adhere to industry standards similar to those in the CGTP final rule. There are currently 11 semen banks accredited by the AATB and, according to industry consultants, the remaining commercial semen banks are licensed by State health agencies, including the California Department of Health and the New York Department of Health.

Semen banks and andrology laboratories at ART establishments are also regulated under the Clinical Laboratory Improvement Amendment (CLIA) of 1988.

The Committee on Laboratory Accreditation and JCAHO also inspect embryo laboratories for accreditation. The requirements for accreditation by the College of American Pathologists (CAP), which accredits ART establishments, closely resemble those in the CGTP final rule, with a few exceptions. Consultants estimate that as many as 80 percent of ART establishments may currently comply with the CAP requirements.

TABLE 3.--ESTIMATED PERCENTAGE OF ESTABLISHMENTS THAT FOLLOW VOLUNTARY INDUSTRY STANDARDS

Affected Industry	Relevant Voluntary Industry Standards	Percentage of Firms Following Voluntary Industry Standards
Eye Tissue: 134 FDA Registered Establishments	EBAA	100 %
Conventional Tissue: (e.g., pericardium, dura mater, heart valves, skin allograft, bone allograft, fascia, tendons, ligaments, other viable) 166 FDA Registered Establishments	AATB	75 to 80 %

TABLE 3.--ESTIMATED PERCENTAGE OF ESTABLISHMENTS THAT FOLLOW VOLUNTARY INDUSTRY STANDARDS

Affected Industry	Relevant Voluntary Industry Standards	Percentage of Firms Following Voluntary Industry Standards
Stem/Progenitor Cells:		
Peripheral Blood (PB): 400 establishments	AABB or FACT	85 % of accredited PB establishments
Cord Blood (CB): 25 establishments	AABB or FACT	100 % of all CB establishments
Reproductive Tissue: Semen Banks: 110 establishments	AATB; CAP accreditation; State Licensed (e.g., NY, CA); and/or CLIA-certified	20 largest establishments (accounting for 95% of total production)
Reproductive Tissue: ART Establishments: 400 establishments	CAP accreditation; State Licensed (e.g., NY, CA); ASRM guidelines	80 %

2. Estimated Impact on Eye Banks, Conventional Tissue Banks and Hematopoietic Stem/Progenitor Cell Establishments

In the sections that follow, the agency considers each of the provisions of this final rule and estimates the impact on establishments in those sectors of the HCT/P industry subject to CGTPs in their entirety. The impact analysis distinguishes expected cost impacts based on both facility size and estimated rates of current adherence to voluntary industry standards. Based on size standards established by the U.S. Small Business Administration (SBA), a small establishment in this industry sector (the North American Industry Classification Scheme (NAICS) code 621991, Blood and Organ Banks) has annual receipts of less than $8.5 million (Refs. 21 and 22).

TABLE 4.--ESTIMATED COST PER ESTABLISHMENT AND ESTIMATED PERCENTAGE OF ESTABLISHMENTS AFFECTED BY THE CGTP FINAL RULE[1]

21 CFR Section	Title	Eye Tissue Establishments	Conventional Tissue Sm./Lrg.	Stem/ Progenitor Cell Establishments

TABLE 4.--ESTIMATED COST PER ESTABLISHMENT AND ESTIMATED PERCENTAGE OF ESTABLISHMENTS AFFECTED BY THE CGTP FINAL RULE[1]

21 CFR Section	Title	Eye Tissue Establishments	Conventional Tissue Sm./Lrg.	Stem/ Progenitor Cell Establishments
1271.150	Current Good Tissue Practice Requirements	--	--	--
1271.155	Exemptions and Alternatives	--	--	--
1271.160	Establishment and Maintenance of a Quality Program: General			
	-Establishment with Minor Deficiencies	$511	$511/$1,278	$511
	-Establishment with Major Deficiencies	(95%)	(23%)	(80%)
	-Cost for Additional Quality Control Work	$2,498	$2,498/$4,832	$2,498
	Procedures for Sharing Information	(5%)	(5%)	(5%)
	Corrective Actions	$1,344	$1,344	$1,344
		(95%)	(23%)	(80%)
(b)(2)	Investigations	$380	$760/$2172	$760
		(95%)	(23%)	(80%)
(b)(3)	Audits	$456	$912	$912
		(95%)	(23%)	(80%)
(b)(6)	Validate Custom Computer Software	$2,214	$2,214	$2,214
		(95%)	(23%)	(80%)
(c)		$456	$912/$1,824	$912
		(95%)	(23%)	(80%)
(d)		$2,160	$2,160	$2,160
		(10%)	(10%)	(10%)
1271.170	Organization and Personnel:			
(b)	Competent Personnel	--	$15,560	$15,560
			(23%)	(95%)
(c)	Training	--	$2,476/$3,104	$2,476
			(23%)	(95%)
1271.180	Procedures--General Requirements	$9,120	$9,120	$9,120
		(5%)	(23%)	(95%)
1271.190	Establishments:			
(d)(1)	Cleaning and Sanitation Procedures	$348	$348/$532	$348
	Cleaning and Sanitation	(5%)	(23%)	(95%)
(d)(2)	Records	--	--	--
1271.195	Environmental Control and Monitoring:			
	Environmental Control			
(a)		--	$348/$532	$348
	Inspections and Monitoring		(23%)	(95%)
(b)(c)		$1,000	--	$1,000
	Records	(5%)		(95%)
(d)		$174	$174/$348	$174
		(95%)	(23%)	(95%)
1271.200	Equipment:			
(b)	Procedures/Schedules--Cleaning, Sanitizing and Maintenance	--	$1,460/$2,979	$1,460
				(95%)
(c)	Calibration	--	(23%)	$1,460
			$1,460/$2,979	(95%)
(d)	Inspections	$216		$216
		(95%)	(23%)	(95%)
(e)	Records		$432/$684	

TABLE 4.--ESTIMATED COST PER ESTABLISHMENT AND ESTIMATED PERCENTAGE OF ESTABLISHMENTS AFFECTED BY THE CGTP FINAL RULE[1]

21 CFR Section	Title	Eye Tissue Establishments	Conventional Tissue Sm./Lrg.	Stem/ Progenitor Cell Establishments
	-of Cleaning, Sanitizing and Calibration Activities	$174 (95%)	(23%)	$174 (95%)
	-of the Use of Each Piece of Equipment	$696 (95%)	$348/$696 (23%) $1,392/$2,784 (23%)	$1,392 (95%)
1271.210	Supplies and Reagents:			
(a)	Verification	$131 (95%)	$348/$532 (23%)	$348 (95%)
(c)	In-house Reagents	--	$348/$532 (23%)	$348 (95%)
(d)(1)	Records of Receipt, Verification, and Lot	$174 (95%)	$174/$348 (23%)	$174 (95%)
1271.220	Process Controls: In-Process Monitoring Procedures	$380 (95%)	$380/$1,086 (23%)	$760 (95%)
1271.225	Process Changes: Validation of Process Changes	$760 (95%)	$760/$2,172 (23%)	$760 (95%)
	Records/Documentation	$456 (95%)	$456/$912 (95%)	$456 (95%)
1271.230	Process Validation:			
(a)	General	$1,700 (95%)	$1,700 (95%)	$1,700 (95%)
	Procedures	$1,520 (95%)	$760/$2,172 (95%)	$1,520 (95%)
(c)	Validation/Revalidation of Process Changes	$850 (95%)	$1,700 (95%)	$1,140 (95%)
1271.250 (a)(b)	Labeling Controls: Procedures	$380 (5%)	$380/$1,086 (5%)	$380 (95%)
1271.260	Storage	--	--	--
1271.265	Receipt, Pre-Distribution Shipment and Distribution:			
	Recordkeeping and Documentation	$864 (5%)	$1,728/$3,456 (5%)	$3,456 (5%)
(a)	Procedures--Receiving Activities	--	(5%)	$760 (95%)
	Procedures--Availability for Distribution		$380/$1,086 (23%)	
(c)	Packaging and Shipping	--	$380/$1,086 (23%)	$760 (95%)
(d)	Procedures--Return to Inventory	$1,392 (95%)	$1,392 (95%)	$576 (95%)
(f)		--	$348/$532 (23%)	$348 (95%)
1271.270	Records:			
(a)	General	$728 (95%)	$728/$1,618 (95%)	$728 (95%)
(b)	Records Management System	$3,040 (95%)	$3,040/$6,080	$3,040 (95%)

TABLE 4.--ESTIMATED COST PER ESTABLISHMENT AND ESTIMATED PERCENTAGE OF ESTABLISHMENTS AFFECTED BY THE CGTP FINAL RULE[1]

21 CFR Section	Title	Eye Tissue Establishments	Conventional Tissue Sm./Lrg.	Stem/ Progenitor Cell Establishments
(d)	Length of Retention	$18 (5%)	(23%) $18 (23%)	$18 (95%)
1271.290	Tracking:			
(b)(c)	System of Product Tracking: General Requirements	$760 (5%)	$380/$1,086 (23%)	$380 (95%)
(d)(e)	System of Product Tracking: Specific Requirements	$1,728 (5%)	$3,456/$6,912 (23%)	$3,456 (95%)
(f)	Consignees	$1,520 (5%)	$1,520 (23%)	$1,520 (95%)
1271.320	Complaint File:			
(a)	Procedures	$131 (95%)	$348/$532 (23%)	$348 (95%)
(b)	Complaint File	--	--	--
(c)	Review and Evaluation of Complaints	$608 (95%)	$608/$1,216 (23%)	$608 (95%)
1271.350	Reporting	$592 (100%)	$592 (100%)	$592 (100%)
1271.370	Labeling	--	--	--
1271.400 (a)	Inspections General	$768 (100%)	$768 (100%)	$768 (100%)
1271.420	HCT/Ps Offered for Import	--	--	--
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	--	--	--

[1] Only subsections expected to impose new compliance costs for a particular industry sector are shown. No cost is estimated for a subsection if analysis revealed that the requirements: (1) do not apply, (2) have no new cost impact, or (3) are met by another subsection of the CGTP final rule. Estimated noncompliance rates are in parentheses.

As indicated by the information in table 4 of this document, the impact of the CGTP final rule varies significantly, depending upon the sector of the HCT/P industry, size of the affected entity and the particular provision. For many of the CGTP provisions, the establishment level impact will entail development of new procedures, or revision of existing procedures. The scope and degree of complexity of these changes will vary. FDA expects that the staff typically involved in the

development, revision, and finalization of establishment procedures will include technicians, clerical staff, lab supervisors, and the lab director. Although FDA did not specify personnel requirements for individual provisions of the CGTP final rule, for purposes of industry-wide estimation, the agency's cost analysis relies on standardized estimates of the type of personnel, level of effort, and hourly labor cost for revising or establishing each type of procedure. Table 5 of this document summarizes the agency's assumptions, which are based on published wage and benefits data and input from HCT/P industry consultants.[1]

Table 5.--Estimated Level of Effort and Cost Per Procedure Revised or Prepared to Comply With the CGTP Final Rule

Category:	Minor Procedures		Major Procedures	
Small Establishment	Revise Existing	Prepare New	Revise Existing	Prepare New
Total level of staff effort	3 hrs.	7 hrs.	8 hrs.	16 hrs.
Cost (rounded)	$131	$348	$380	$760
Large Establishment				
Total level of staff effort	5 hrs.	13 hrs.	27 hrs.	54 hrs.
Cost (rounded)	$192	$532	$1,086	$2,172

The analysis of cost impacts for HCT/P industry sectors subject to CGTPs in their entirety is summarized in the following discussion of the rule's individual provisions, and the expected type and extent of industry impact. The pertinent section of the final rule is noted to facilitate reference to

[1] A detailed presentation of level of effort and cost assumptions for nonreproductive tissue establishments is provided in FDA's Cost Impacts of the Proposed Current Good Tissue Practice Rule on Eye Banks, Conventional Tissue Banks, and Stem Cell Facilities: Background Paper, April 1999, and for reproductive tissue facilities in Cost Impacts of the Proposed Current Good Tissue Practice Rule on Semen Banks and ART Facilities, February 1999, prepared by Eastern Research Group (ERG), Inc. These documents are available in docket 97N-484P.

the related cost estimates presented in table 4 of this document.

a. Section 1271.150--current good tissue practice: general. The final rule requires manufacturers of HCT/Ps to follow CGTPs. Section 1271.150(a) provides an overview of CGTPs but does not present specific compliance requirements. The specific requirements are addressed in subsequent sections. Section 1271.150(b) lists the core CGTP requirements, and § 1271.150(c) addresses compliance with applicable requirements for those entities subject to CGTPs. Section 1271.150(d) explains the relationship between the CGTP rule and regulations specifically applicable to biological drugs or devices, and paragraph (e) defines the term "where appropriate" in relation to the rule. Section 1271.150(b) through (e) will not generate any compliance costs for the HCT/P industry because no specific requirements are specified.

b. Section 1271.155--exemptions and alternatives. The CGTP final rule allows establishments to request an exemption or alternative from FDA for certain provisions of the rule. There is currently no basis for predicting the number of industry requests for exemptions or alternatives, or for predicting the effect of these actions on compliance costs. Because of a high degree of similarity between CGTPs and current voluntary industry standards, FDA anticipates that very few establishments

will consider it appropriate to be exempted from the provisions of this final rule.

c. Section 1271.160--establishment and maintenance of a quality program. The final rule requires that establishments establish and maintain a quality program. The quality program must include: Procedures relating to core CGTP requirements, procedures for exchanging information with other establishments known to have recovered cells or tissue from the same donor, appropriate corrective actions related to core CGTP requirements, proper training and education of personnel involved in activities related to core CGTP requirements, appropriate monitoring systems, investigation and documentation of HCT/P deviations related to core CGTP requirements, audits, computer software validation or verification, and other procedures specific to the quality program. Several of these functions are further specified in subsequent provisions of the rule, and the impact is estimated in the context of those provisions.

In general, FDA anticipates that almost all of the establishments in the affected industry sectors have the appropriate facilities, equipment, and systems to support a quality program, but only those already following industry standards are expected to have comprehensive quality programs in place. Some establishments may need to upgrade their quality

program for several of the CGTP requirements. These include procedures for sharing information, corrective actions, and investigations. Further, some establishments may need to take additional steps to administer corrective actions and conduct investigations if they currently do so only when major deficiencies arise.

Although the sharing of information is an industry-wide practice, some small establishments, particularly those not following current industry standards, may not have written procedures and forms for this task. FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks not following the current AATB standards, and 80 percent of the hematopoietic stem/progenitor cell establishments not following the FACT or AABB standards, will need to prepare a major procedure to address this requirement.

Although FDA anticipates that most industry establishments take steps to administer corrective actions and conduct investigations, some may currently do so only when major deficiencies arise.

FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks, and 80 percent of hematopoietic stem/progenitor cell establishments not following industry standards will need to invest additional time to meet these new requirements. The incremental time burden to administer

corrective actions and document these activities is estimated to be an additional 1/2-hour per month of laboratory director time at establishments that already perform this activity to a lesser extent, and an additional hour per month at all other establishments that will be newly affected by this provision. As discussed in the background papers prepared by FDA and Eastern Research Group (ERG), and shown in table 4 of this document, for newly required investigations in tissue establishments, FDA estimates an additional cost per year of $2,214 for an additional 2 hours per month for the laboratory director to investigate and document deficiencies, and an additional 1/2 hour each for the laboratory supervisor and lab technician to participate in the investigations.

A number of establishments will also need to institute other requirements of the quality program, including periodic audits, computer software validation or verification, and procedures specific to the quality program. Audits are part of the industry standards published by the AATB, EBAA, FACT, and AABB. However, some establishments following these standards may need to do some additional recordkeeping, and establishments not following standards will need to begin to conduct audits. Referring to table 4 of this document, FDA assumes that up to 95 percent of eye banks will increase their audit efforts, including additional lab director time to prepare for and

perform the periodic audit. An estimated 23 percent of conventional tissue banks will allocate additional resources for audits, with a higher allocation of hours at larger establishments, to prepare for, and to conduct, the audit. For hemapoietic stem/progenitor cell establishments, FDA estimates that there will be no additional auditing required at establishments following FACT or AABB standards, but an estimated 80 percent of establishments not following industry standards will need to spend additional time to prepare for and to conduct periodic audits.

Section 1271.160 of the CGTP final rule further stipulates that establishments must validate or verify, as appropriate, the computer software used in their operations when it is used in the performance of core (good tissue practice (GTP) functions. Validation would be required for custom software used in core GTP functions. However, for off the shelf commercial software packages (e.g., for data storage and retrieval, recordkeeping, etc.) used as intended by the software manufacturer, it would be adequate for the establishment, when using such products in the performance of core GTP functions, to verify the product's performance. Such products are already validated or verified by the software vendor.

FDA assumes that none of the affected establishments currently validate or verify their custom software and that

approximately 10 percent of eye banks, conventional tissue banks and hematopoietic stem/progenitor cell establishments have developed custom software that will require full validation or verification under this final rule. Because we received no specific comments regarding these assumptions in response to the proposed rule, we have retained them here. Although the scope of such work can vary, FDA estimates that the custom software in use has a limited scope of application, and that an average of 60 hours of work by the laboratory supervisor will be required to validate or verify custom computer software at an establishment. Detailed presentations of these assumptions are provided in section 2.4.3 of the background papers (see footnote 1 of this document) by FDA and ERG.

The last requirement for the quality control program is for procedures that stipulate how the quality program should be operated. Industry consultants indicated that establishments have quality systems in place, but that most establishments are not aware of some minor elements of CGTPs that should be included in their procedures. Consequently, inspectors for accreditation groups often find a few deficiencies during initial visits. FDA estimates that about 95 percent of eye banks, 23 percent of conventional tissue banks, and up to 80 percent of hematopoietic stem/progenitor cell establishments will have minor deficiencies that will require them to revise

one minor and one major procedure. In addition, FDA estimates that 5 percent of all eye banks, and conventional tissue banks and hematopoietic stem/progenitor cell establishments not following voluntary industry standards may identify major deficiencies, and will need to prepare five minor procedures and one major procedure to address those problems.

The agency further assumes that establishments may generally need to perform some additional quality control work to comply with the quality program requirements in the CGTP final rule. Although some tasks will not require any additional time to perform, FDA estimates that approximately 1 hour per month each for the laboratory director and supervisor may be needed. The agency estimates that 95 percent of all eye banks, 23 percent of conventional tissue banks, and approximately 80 percent of hematopoietic stem/progenitor cell establishments will need to allocate additional staff time for this purpose.

d. Section 1271.170--personnel. This final rule requires establishments to employ sufficient personnel with the necessary education, experience, and training to ensure competent performance of their assigned functions. The EBAA, AATB, FACT, and AABB standards for quality assurance all include provisions for appropriate personnel qualifications and training, and recordkeeping related to this requirement. It is expected that most eye banks, conventional tissue banks and hematopoietic

stem/progenitor cell establishments will already be compliant with these provisions of the CGTP rule. Those establishments in the conventional tissue and hematopoietic stem/progenitor cell manufacturing sectors that do not follow industry standards will incur new costs. The cost of this staffing effort is estimated to be approximately $15,560 per affected establishment.

FDA anticipates that the 23 percent of conventional tissue banks and 95 percent of hematopoietic stem/progenitor cell establishments not following industry standards will incur new training costs to comply with the personnel provisions of the CGTP final rule. For a small tissue establishment, these costs are estimated to average $2,476. The CGTP final rule also requires that records of personnel qualifications and training be maintained, but because existing industry standards address personnel recordkeeping, FDA assumes that the cost to comply with this requirement will be negligible. Details of these assumptions are provided in section 2.4.4 of the background papers (see footnote 1 of this document) by FDA and ERG.

e. Section 1271.180--procedures: general requirements. The CGTP final rule requires establishments to establish and maintain written procedures appropriate to meet core CGTP requirements for all steps performed in the manufacture of HCT/Ps. FDA anticipates a negligible incremental cost for most establishments following industry standards, and an additional

120 hours of laboratory director time for establishments not following the current industry standards. FDA estimates that 5 percent of eye banks will need to expand their current efforts, and that 23 percent of conventional tissue banks and 95 percent of hematopoietic stem/progenitor cell establishments will incur new costs.

f. Section 1271.190--facilities. This final rule stipulates a number of requirements regarding facilities covering operations, size, construction, location, lighting, ventilation, plumbing, drainage and access to sinks and toilets. A facility used in the manufacture of HCT/Ps must be of suitable size, construction, and location to prevent contamination of HCT/Ps with communicable disease agents and to ensure orderly handling of HCT/Ps without mix-ups. Cleaning and sanitation requirements are also outlined, including requirements for written procedures, schedules, and documentation of these activities.

Based on discussions with industry experts, FDA estimates that nearly all establishments that follow industry standards will not incur any new costs under these provisions of the CGTP final rule. However, some establishments that generally adhere to cleaning standards do not have written procedures. Thus, FDA estimates that 5 percent of all eye banks, in addition to 23 percent of the conventional tissue banks and 95 percent of all

hematopoietic stem/progenitor cell establishments, will incur the cost of writing a minor procedure for cleaning. The facilities provision of the CGTP final rule also requires that records of cleaning be maintained. This requirement is met by establishments following industry standards, and is expected to have a negligible impact on establishments not following the current voluntary standards.

g. Section 1271.195--environmental control and monitoring. Where environmental conditions could reasonably be expected to cause contamination or cross-contamination, or accidental exposure of HCT/Ps to communicable disease agents, environmental conditions must be adequately controlled. The final rule also requires that environmental control systems be monitored and periodically inspected, and that environmental control and monitoring activities be documented. The impact of this provision of the CGTP rule varies by industry sector. For affected eye banks, the EBAA standards already contain similar provisions, however, some additional costs may be incurred for periodic inspection of environmental control systems and for keeping records of environmental control and monitoring activities. It is estimated that 5 percent of eye banks may incur new costs for inspection of equipment. FDA anticipates that conventional tissue banks following AATB standards will experience no new costs, but that the remaining 23 percent of

establishments will need to prepare a minor procedure for control and monitoring of ventilation and air filtration.

The current FACT and AABB standards do not require written procedures for environmental control and monitoring. FDA therefore estimates that 95 percent of all hematopoietic stem/progenitor cell establishments will need to develop a minor procedure for control and monitoring of ventilation and air filtration systems to comply with the CGTP rule. However, because the industry standards do provide for appropriate environmental controls, FDA assumes that some establishments are performing the necessary control and monitoring activities. The agency estimates that as many as half of the establishments currently following industry standards may already be conducting routine inspections of their environmental control equipment. It is assumed that the remaining 50 percent of those establishments, and 95 percent of hematopoietic stem/progenitor cell establishments assumed not to be following industry standards, will incur additional costs to periodically inspect equipment and perform recordkeeping related to environmental control. Table 4 of this document provides estimates of cost per establishment associated with these efforts.

h. Section 1271.200--equipment. This final rule requires that appropriate equipment be used in processing HCT/Ps to prevent the introduction, transmission, or spread of

communicable disease. Cleaning, sanitizing, maintenance, and calibration of equipment must be performed according to established schedules and procedures; equipment must be regularly inspected for adherence to applicable procedures and schedules; and all such activities must be documented. In addition, establishments must keep records of each use of each piece of equipment, including the identification of each HCT/P manufactured with that piece of equipment.

The standards related to equipment, as specified by AATB, EBAA, FACT, and AABB, generally address maintenance procedures, and recordkeeping related to maintenance. However, this final rule extends beyond industry standards of EBAA, FACT, and AABB in the areas of equipment inspection and recordkeeping. Based on information provided by industry sources, FDA believes that some of the larger HCT/P establishments may already be performing the required equipment inspection and recordkeeping.

FDA therefore estimates that 95 percent of all eye banks will allocate an additional 1/2-hour per month for the laboratory supervisor to inspect equipment, an additional 1/2-hour per month of technician time to document equipment cleaning and calibration, and 2 additional hours per month for a technician to record each use of the equipment.

The estimated 23 percent of conventional tissue banks that currently do not follow AATB standards will also incur new costs

related to the equipment provisions. FDA estimates that small establishments will prepare one minor procedure for calibration, and for cleaning and other maintenance for each of six pieces of equipment. In addition, small establishments will allocate an additional hour per month of lab supervisor time for routine inspection of equipment, an additional hour per month of technician time for documentation of cleaning and calibration, and 4 hours per month of technician time to record each use of the equipment. FDA estimates that large establishments will need to write minor procedures for each of eight pieces of equipment, will allocate an additional 2 hours per month of lab supervisor time for routine inspection of equipment, an additional 2 hours per month of technician time to record cleaning and calibration activities, and an additional 8 hours of technician time per month to record each use of each piece of equipment. It is anticipated that establishments simultaneously preparing multiple procedures related to equipment will realize some economies of scale because of similarities across procedures. This is expected to result in a savings of 30 percent in the total amount of staff time required to prepare six to eight minor equipment maintenance procedures.

It is expected that hematopoietic stem/progenitor cell establishments will also be required to perform additional work to align current practice with the CGTP requirements. Current

FACT procedures provide for routine maintenance and calibration of equipment. In addition, the AABB standards recommend that SOPs be established for proper equipment maintenance and monitoring. To further develop procedures to address routine maintenance and recordkeeping under the CGTP rule, FDA estimates that 95 percent of all hematopoietic stem/progenitor cell establishments will prepare a minor procedure for calibration of each of six pieces of equipment. In addition to the preparation of procedures, lab personnel will be involved in carrying out the necessary maintenance work, estimated to require an additional 1/2 hour of lab supervisor time per month for routine inspection of equipment, an additional 1/2 hour per month for lab technicians to document cleaning and calibration work, and an additional 4 hours per month of lab technician time to record each use of equipment. In addition, most cell establishments that do not currently follow FACT or AABB standards will incur the cost of preparing a minor procedure for cleaning and sanitizing, and for routine maintenance of each of six pieces of equipment. Section 2.4.8 of the FDA and ERG background papers (see footnote 1 of this document) provide detailed presentations of these assumptions.

i. Section 1271.210--supplies and reagents. The CGTP rule requires manufacturers to verify that supplies and reagents used in the manufacture of HCT/Ps meet specifications designed to

prevent circumstances that increase the risk of introduction, transmission, or spread of communicable disease. Verification of quality may be accomplished by the establishment that uses the supply or reagent, or the vendor of the supply or reagent. This final rule also requires documentation of the receipt and verification of supplies or reagents used in HCT/P processing, and of the lot of supply or reagent used in the manufacture of each HCT/P.

The existing industry standards address some or all of these activities, and the estimated impact per establishment varies accordingly. EBAA standards specify that sterilized supplies and reagents must contain sterilization dates and method, or appropriate expiration dates. However, the agency estimates that up to 95 percent of eye banks will need to devote additional resources to receipt and verification activities, and will devote additional staff time to recording the receipt of supplies and reagents. Similarly, FACT and AABB standards contain provisions for quality control in the storage, handling and use of supplies and reagents, including maintenance of records. However, FDA expects that approximately 95 percent of hematopoietic stem/progenitor cell establishments will expand on their current supply and reagent related recordkeeping to comply with these CGTP provisions.

The current AATB standards address most of the requirements for supplies and reagents included in the final rule. FDA assumes that the estimated 23 percent of conventional tissue establishments that do not follow these standards will require additional resources for in-house reagent receipt and verification, and will devote additional staff time to keeping records of the receipt and verification of supplies and reagents. The estimated costs per establishment for these provisions are presented in table 4 of this document.

j. Section 1271.215--recovery. The CGTP final rule requires that each HCT/P be recovered in a way that does not cause contamination or cross contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the HCT/P. Because this section does not impose any specific requirements it is not expected to impose any identifiable compliance costs.

k. Section 1271.220--processing and process controls. The CGTP final rule requires establishments to process HCT/Ps in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease. An establishment processing HCT/Ps is responsible for ensuring that each in-process HCT/P is controlled until the results of any required inspections, testing, verification activities or

approvals are received and documented. The standards for tissue banking specified by the AATB include activities to address these process controls, but the EBAA, FACT, and AABB standards do not include specific requirements for in-process monitoring. FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks, and 95 percent of hematopoietic stem/progenitor cell establishments will need to prepare a minor procedure related to process monitoring.

1. Section 1271.225--process changes. This final rule requires establishments to verify or validate any changes to established procedures to ensure that the change does not create an adverse impact elsewhere in the operation. Process changes must be approved before implementation by a responsible person and approved changes must be communicated to appropriate personnel in a timely manner. The current standards for AATB, FACT, and the AABB provide for SOPs for process changes, although recordkeeping procedures are not specified. Current EBAA standards do not provide for SOPs for process changes. FDA therefore estimates that nearly all eye banks will need to prepare a major procedure for process changes, and will allocate an additional 1/2 hour of lab director time to document process changes.

FDA anticipates that the 23 percent of conventional tissue banks not following the AATB standards will need to prepare a

major procedure related to process changes, and that nearly all tissue banks will increase related recordkeeping. The agency estimates that small conventional tissue banks will spend an additional 1/2 hour per month of lab director time to document process changes, and that large establishments would allocate an additional hour of lab director time per month for this activity. FDA anticipates that almost all hematopoietic stem/progenitor cell establishments that do not follow FACT or AABB standards will need to prepare a major procedure to address process changes. In addition, FDA estimates that 95 percent of all hematopoietic stem/progenitor cell establishments will also allocate an additional half hour of lab director time per month to document process changes. The associated costs per establishment are presented in table 4 of this document.

m. Section 1271.230--process validation. This final rule requires establishments to validate processes that cannot be verified through subsequent inspection and testing, and that the validation activities and results be documented. Current EBAA standards do not require process validation. Based on information provided by industry sources, FDA believes that some of the larger eye banks may already be performing the required process validation. Although current AATB, FACT, and AABB standards include provisions for process validation and related recordkeeping, industry experts indicate that additional

validation work will be required at nearly all establishments under the CGTP final rule. FDA therefore estimates that 95 percent of all eye banks, conventional tissue banks, and all hematopoietic stem/progenitor cell establishments not following AABB or FACT voluntary standards, will prepare two major procedures related to process validation, and 95 percent of conventional tissue banks and hematopoietic stem/progenitor cell establishments will revise two major procedures. Further, FDA estimates that 95 percent of all establishments in each sector of the HCT/P industry will devote additional staff time to perform process validation. Details of these assumptions are provided in section 2.4.12 of the background papers (see footnote 1 of this document) by ERG and FDA.

In addition to the initial validation work, the CGTP final rule requires revalidation when changes to a validated process occur. The agency estimates that approximately 95 percent of eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments will need to allocate an additional 20 to 40 hours of laboratory staff time annually for procedure revalidation. Costs for these provisions of the CGTP rule are presented in table 4.

n. Section 1271.250--labeling controls. The CGTP rule requires establishments to establish and maintain written procedures for controlling the labeling of products. These

procedures must ensure proper identification of products and include various checks and verifications. Each product must also be accompanied by a summary of donor eligibility information, if applicable.

According to consultants and industry contacts, labeling controls are usual and customary practice in all sectors of the HCT/P industry. FDA anticipates that only about 5 percent of eye banks, conventional tissue banks and hematopoietic stem/progenitor cell processing establishments will need to perform additional work to comply with the CGTP labeling controls. FDA estimates that such establishments will need to revise a major procedure for proper identification of products.

o. Section 1271.260--storage. The CGTP final rule requires that storage areas be controlled to prevent mixups, contamination, cross-contamination, and to prevent an HCT/P from being improperly made available for distribution. Temperature must be monitored and limits established, including expiration dating where appropriate. Each of the relevant HCT/P industry standards contains provisions regarding storage practices. Based on agency review of current industry standards, and conversations with experts about current practices at HCT/P establishments, FDA anticipates that virtually all establishments already comply with these provisions of the CGTP rule. These provisions are therefore expected to produce no new

cost impact for eye banks, conventional tissue banks and hematopoietic stem/progenitor cell processing establishments.

p. Section 1271.265--receipt, predistribution shipment, and distribution. The CGTP final rule requires that procedures be established and maintained for receipt (e.g., determination of whether to accept, reject, or place the HCT/P in quarantine), predistribution shipment, and distribution of HCT/Ps. Documentation of each of the aforementioned activities, when performed, is also required. Packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination, and appropriate shipping conditions must be established and maintained during transit. Procedures must also be established to determine whether products returned to an establishment are suitable to be returned to inventory. Agency review of current industry standards indicates that most provisions related to this area of quality control are included in each of the relevant industry standards.

The primary impact of the CGTP provisions for product receipt, predistribution shipment, and distribution, thus, involves procedures development for establishments that do not currently follow industry standards. FDA estimates that 5 percent of eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments will increase lab supervisor time to document the receipt of products.

The agency estimates that conventional tissue banks not following AATB standards will need to revise one major procedure for receiving products, revise one major procedure related to distribution of products, and prepare a minor procedure for return of products to inventory. FDA estimates that 95 percent of hematopoietic stem/progenitor cell establishments will write one major procedure addressing receiving activities. Establishments following FACT or AABB standards will also need to revise a major procedure for product distribution, while all other establishments will need to prepare a new major procedure for product distribution, as well as a minor procedure for the handling of products returned to inventory. Details of these assumptions are presented in section 2.4.15 of the background papers (see footnote 1 of this document) by ERG and FDA and the estimated costs per establishment for these activities are presented in table 4 of this document.

q. Section 1271.270--records. The CGTP rule requires that records be maintained for all steps required in this subpart and subpart C of this part. A records management system relating only to core CGTP requirements must be established and maintained. Records pertaining to a particular HCT/P must be maintained for at least 10 years after the date of administration, if known, or at least 10 years after the date of the HCT/P's distribution, disposition or expiration, whichever

is latest. This final rule also requires that records be kept of any contracts or agreements. Although many components of the required recordkeeping system are addressed under individual provisions of the CGTP rule, there may be a few minor gaps in the records system of an establishment that would be addressed under this general provision. The agency therefore estimates that approximately 95 percent of all eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments that do not follow FACT or AABB standards, will write at least one minor procedure, and revise one major procedure related to recordkeeping.

The agency also estimates that additional lab director time will be allocated (an estimated 40 hours at small establishments and 80 hours at large establishments) to set up enhanced recordkeeping where a system is already in place. System enhancement will be performed at an estimated 95 percent of eye banks, 23 percent of conventional tissue banks and 95 percent of hematopoietic stem/progenitor cell establishments.

Various industry standards specify record retention, although the time periods vary somewhat. Of those establishments following industry standards, approximately 95 percent of eye banks and 75 percent to 80 percent of conventional tissue banks retain records for at least 10 years, and the remainder retain records for a minimum of 5 years. For

these establishments, and the hematopoietic stem/progenitor cell establishments that do not currently follow industry standards, FDA estimates increased record retention costs based on the cost of storing an additional five boxes (2.4 cubic feet each) of records per year for 5 years. The estimated record retention costs should be viewed as maximum potential burdens since affected entities have the option to retain the required records in more cost-effective (e.g., electronic) formats and because some establishments already retain records for 10 years.

The retention standards of FACT and AABB for records related to products are different from those concerned with facility and equipment maintenance, and personnel education and training. All records related to hematopoietic stem/progenitor cell products must be retained indefinitely whereas records related to facility and equipment maintenance and personnel training must be retained for only 5 years.

FDA estimates that half of the records at hematopoietic stem/progenitor cell establishments following industry standards will need to be retained for an additional 5 years, and that the annual cost will be comparable to that of other small eye banks and conventional tissue banks. The agency also estimates that nearly all hematopoietic stem/progenitor cell establishments that are not following industry standards will need to increase record retention efforts. Almost all hematopoietic

stem/progenitor cell establishments that do not follow industry standards are also expected to prepare at least one minor procedure and to revise a major procedure related to recordkeeping. The laboratory director at these establishments is expected to allocate 40 hours of additional time to improving the establishment's current recordkeeping system.

r. Section 1271.290--tracking. This final rule stipulates the steps needed to properly track a product from donor to consignee or final disposition and vice versa. The CGTP rule requires that establishments maintain a method for product tracking and that each product is assigned and labeled with a distinct identification code (identifier). If a new identifier is assigned during the manufacturing process, procedures must be in place for relating the new identifier to the old identifier. The establishment that manufactured the product must also keep track of the disposition of each product, so that the consignee can be easily identified. Establishments must also inform consignees in writing of the requirements of this section and of the established tracking method. In addition, labeling must include information designed to facilitate effective tracking from the donor to the recipient and from the recipient to the donor.

Product "traceability" is a familiar concept and common practice in the eye banking, conventional tissue and

hematopoietic stem/progenitor cell processing industries. Eye banks following EBAA standards maintain records with information that permits tracing of product from the donor source to the patient recipient, working through the surgeon who performed the procedure. FDA anticipates that only 5 percent of eye banks will need to enhance current tracking systems, prepare one major procedure related to product tracking, spend additional staff time each month to identify and document consignee information, and allocate additional laboratory director time to inform the consignees who receive products and ensure the tracking requirements are met.

Conventional tissue banks following AATB standards are able to trace all products from donation source to product recipient. Conventional tissue establishments not following AATB requirements will need to revise a major procedure to address product tracking, and to allocate additional staff time each month to obtain and record information about product consignees.

The FACT and AABB standards for product tracking in hematopoietic stem/progenitor cell establishments recommend that the establishment be able to trace products to final distribution or disposition, but do not specify that formal agreements be established with consignees to assure timely tracking of products. FDA therefore estimates that 95 percent of hematopoietic stem/progenitor cell establishments will, on a

one-time basis, allocate an additional 20 hours of laboratory supervisor time to inform consignees who will receive products of tracking systems and requirements. In addition, FDA estimates that 95 percent of hematopoietic stem/progenitor cell establishments that are not following FACT or AABB standards will need to revise a major procedure related to product tracking, and will need to allocate additional staff hours each month for consignee documentation. The estimated costs per establishment to perform these activities are presented in table 4 of this document.

s. Section 1271.320--complaint file. The CGTP final rule requires establishments to maintain procedures for the review, evaluation, and documentation of complaints relating to core CGTP requirements, and the investigation of complaints as appropriate. Establishments are required to review and evaluate complaints as soon as practical and to determine whether each complaint represents an event that must be reported to FDA. Documentation of the review and evaluation is required, even if no reporting is made. FDA finds that the AATB, FACT, and AABB standards explicitly address procedures for, or recordkeeping related to, complaints. Based on discussions with industry experts, the agency anticipates that nearly all establishments currently track, albeit informally, the complaints received from consignees and recipients. Establishments that must prepare new

written procedures for review and handling of complaints would incur additional costs under these CGTP provisions. The agency estimates that the additional costs for establishments to maintain a complaint file would be negligible.

To fully comply with these provisions of the CGTP rule, FDA estimates that 95 percent of all eye banks will revise a minor procedure to include the required handling of complaints, and allocate some additional staff time each year to review complaints. FDA assumes that conventional tissue banks following AATB standards will already be performing the necessary activities, but the estimated 23 percent of establishments not following AATB standards will need to prepare a minor procedure for complaint handling, and allocate additional laboratory director time each year to review any complaints received.

Although the industry standards for hematopoietic stem/progenitor cell processing require that records be maintained of both donor and recipient complaints, the CGTP rule requires that establishments also have written procedures for complaint review. FDA therefore estimates that 95 percent of hematopoietic stem/progenitor cell establishments will write a minor procedure to handle complaints, and that 95 percent of all establishments that do not follow industry standards will also allocate additional time for yearly review and handling of

complaints. Details of these assumptions are presented in section 2.4.18 of the background papers (see footnote 1 of this document) by FDA and ERG.

t. Section 1271.350--reporting. This final rule requires establishments to investigate adverse reaction reports and report to FDA any adverse reactions, involving a communicable disease, that are fatal, life-threatening, result in permanent impairment of the body, or necessitate medical or surgical intervention, including hospitalization. In addition, the final rule requires establishments to investigate all HCT/P deviations and report to FDA any deviation related to core CGTP requirements if the deviation occurs in the establishment's facility or in a facility that performs a manufacturing step under contract, agreement, or other arrangement with the establishment. In our economic analysis of the proposed CGTP rule, we assumed that these provisions would result in negligible new costs for affected entities. However, because these are new FDA reporting requirements, the agency believes that additional costs will be incurred by all eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments. The agency further estimates that a typical affected establishment will submit an average of six Form FDA 3500A (adverse reaction) reports and two Form FDA 3486 (HCT/P deviation) reports per year, requiring an additional 8

hours of laboratory director time. The associated costs are presented in table 4 of this document.

u. Section 1271.370--labeling. The CGTP rule requires that products be labeled clearly and accurately, with information including a description of the HCT/P along with its distinct identification code, the name and address of the manufacturer, a description of the product and the product expiration date. The storage temperature, appropriate warnings, and adequate instructions for use when related to the prevention of the introduction, transmission, or spread of communicable disease must also be provided on the label or on a package insert.

Industry consultants inform FDA that the required elements are typically present on the labels of products manufactured by eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments. Proper labeling is considered very important to these industries, to prevent the misuse of their products. FDA assumes, therefore, that establishments in the various sectors of the HCT/P industry are already compliant with these provisions of the CGTP final rule, and that the cost impact will be negligible.

v. Section 1271.400--inspections. FDA could conduct inspections of any facility subject to the CGTP final rule. FDA will typically interact primarily with one responsible person for each establishment, but other personnel may also be involved

in the inspection. FDA could inspect facilities, equipment, processes, products, procedures, labeling, and records, and could review and copy any records required to be kept under this final rule. The agency estimates that all industry establishments, both domestic and foreign, will be subject to this provision of the CGTP final rule, and inspections will occur periodically. FDA estimates that up to 16 hours of laboratory technician time will be necessary, to accompany the FDA inspector through the facility and to support the inspector's information needs, and that up to 4 hours of laboratory director time will be needed for activities related to the inspection. This is expected to impose a cost of approximately $768 per establishment per inspection.

w. Section 1271.420--HCT/Ps offered for import. The CGTP final rule requires importers of HCT/Ps to notify the FDA district director having jurisdiction over the port of entry through which the HCT/P is imported or offered for import. The HCT/P must be held intact or transported under quarantine until it is inspected and released by FDA. There is currently very limited use of imported HCT/Ps that would trigger activities for compliance with this provision of the CGTP final rule. FDA therefore estimates the current cost for industry compliance with this requirement to be negligible.

x. Section 1271.440--orders of retention, recall, and cessation of manufacturing. Firms in the HCT/P industry may incur costs to comply with orders issued under this provision. There is little available data on which to base estimates of the future frequency and scope of HCT/P industry conditions and practices that would necessitate such actions on the part of FDA. The agency anticipates that orders issued under this provision of the CGTP final rule will be rare. FDA estimates that the yearly costs to the HCT/P industry resulting from such orders will therefore be negligible.

3. Estimated Impact on Reproductive Tissue Establishments

As explained elsewhere in this preamble, establishments involved with reproductive tissue (e.g., ART establishments and semen banks) are subject only to the CGTP inspection and enforcement provisions of § 1271.400 as they apply to donor eligibility requirements under subpart C. The impact of these provisions is described in the following section and the estimated cost impact is presented in table 6 of this document.

TABLE 6.--ESTIMATED COST PER ESTABLISHMENT AND ESTIMATED PERCENTAGE OF REPRODUCTIVE TISSUE ESTABLISHMENTS AFFECTED BY THE CGTP FINAL RULE

21 CFR Section	Title	ART Establishments	Semen Banks
1271.400	Inspections	$768 (100%)	$768 (100%)

a. Section 1271.400--inspections. FDA could conduct inspections of any facility subject to subpart F. This provision affects reproductive tissue establishments only

insofar as it applies to the donor eligibility requirements under subpart C, and not to CGTPs generally. FDA will typically interact primarily with one responsible person for each establishment, but other personnel may also be involved in the inspection. FDA could inspect the donor eligibility related procedures and records of reproductive tissue establishments, and could review and copy any records required to be kept under this final rule.

The agency estimates that all ART and semen bank establishments, whether domestic or foreign, will be subject to this provision of the CGTP final rule, and inspections will occur periodically. FDA estimates that up to 16 hours of laboratory technician time will be necessary, to accompany the FDA inspector through the establishment and to support the inspector's information needs, and that up to 4 hours of laboratory director time will be needed for activities related to the inspection. This is expected to impose a cost of approximately $768 per establishment per inspection. This is the only provision of the CGTP final rule that applies to establishments involved with reproductive tissues.

4. Summary of Estimated One-Time, Annual, and Annualized Cost Impacts

The costs for each section of the CGTP final rule are computed as the product of the estimated number of affected

establishments (table 3 of this document), the estimated compliance cost per establishment, and the estimated percentage of establishments not currently following CGTPs (table 4 of this document), and are presented by HCT/P industry sector in tables 7 through 11 of this document. The total one-time and annual compliance costs, summed over all provisions of the CGTP rule, are also presented by HCT/P industry sector in these tables. The aggregate one-time and annual compliance costs for all sectors of the HCT/P industry are summarized in table 12 of this document. The total annualized cost estimates presented in tables 7 through 12 of this document include both the estimated annual and one-time costs, such as are incurred to prepare new procedures, and are annualized over 10 years using both 7 percent and 3 percent discount rates.

TABLE 7.--AGGREGATE COMPLIANCE COSTS FOR EYE BANKS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs [1]	Total Annualized Costs [2]
1271.150	CGTP Requirements	$0	$0	$0	$0
1271.155	Exemptions & Alternatives	$0	$0	$0	$0
1271.160	Quality Program	$159,038	$569,031	$591,674	$587,675
1271.170	Personnel	$0	$0	$0	$0
1271.180	Procedures	$0	$61,104	$61,104	$61,104
1271.190	Facilities	2,328	$0	$331	$273
1271.195	Environmental Control & Monitoring	$0	$28,550	$28,850	$28,850
1271.200	Equipment	$0	$138,248	$138,248	$138,248
1271.210	Supplies & Reagents	$16,613	$22,150	$24,515	$24,098
1271.215	Recovery	$0	$0	$0	$0
1271.220	Processing and Process Controls	$48,374	$0	$6,887	$5,671
1271.225	Process Changes	$96,748	$58,049	$71,824	$69,391
1271.230	Process Validation	$409,906	$108,205	$166,566	$156,258
1271.250	Labeling Controls	$2,456	$0	$362	$298
1271.260	Storage	$0	$0	$0	$0
1271.265	Receipt, Predistribution Shipment & Distribution	$0	$182,990	$182,990	$182,990
1271.270	Records	$479,603	$121	$68,405	$56,345

1271.290	Tracking	$15,276	$11,578	$13,753	$13,368
1271.320	Complaint File	$16,613	$77,398	$79,764	$79,364
1271.350	Reporting	$0	$81,472	$81,472	$81,472
1271.370	Labeling	$0	$0	$0	$0
1271.400	Inspections	$0	$102,912	$102,912	$102,912
1271.420	HCT/Ps Offered for Import	$0	$0	$0	$0
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	$0	$0	$0	$0
Total	All Sections	$1,247,044	$1,442,108	$1,619,659	$1,588,300

[1] Over 10 years at 7 percent interest.
[2] Over 10 years at 3 percent interest.

TABLE 8.--AGGREGATE COMPLIANCE COSTS FOR CONVENTIONAL TISSUE ESTABLISHMENTS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs [1]	Total Annualized Costs [2]
1271.150	CGTP Requirements	$0	$0	$0	$0
1271.155	Exemptions & Alternatives	$0	$0	$0	$0
1271.160	Quality Program	$127,960	$213,246	$231,464	$228,247
1271.170	Personnel	$594,081	$101,444	$186,028	$171,088
1271.180	Procedures	$0	$348,202	$348,202	$348,202
1271.190	Facilities	$14,838	$0	$2,113	$1,739
1271.195	Environmental Control & Monitoring	$14,838	$8,124	$10,237	$9,863
1271.200	Equipment	$137,313	$101,411	$120,961	$117,508
1271.210	Supplies & Reagents	$29,676	$8,124	$12,349	$11,603
1271.215	Recovery	$0	$0	$0	$0
1271.220	Processing and Process Controls	$20,516	$0	$2,921	$2,405
1271.225	Process Changes	$41,033	$87,940	$93,782	$92,750
1271.230	Process Validation	$437,574	$268,090	$330,391	$319,387
1271.250	Labeling Controls	$4,460	$0	$635	$523
1271.260	Storage	$0	$0	$0	$0
1271.265	Receipt, Predistribution Shipment & Distribution	$55,871	$237,058	$245,012	$243,607
1271.270	Records	$287,965	$687	$41,687	$34,446
1271.290	Tracking	$78,550	$161,361	$172,544	$170,569
1271.320	Complaint File	$14,837	$28,388	$30,500	$30,127
1271.350	Reporting	$0	$100,928	$100,928	$100,928
1271.370	Labeling	$0	$0	$0	$0
1271.400	Inspections	$0	$127,488	$127,488	$127,488
1271.420	HCT/Ps Offered for Import	$0	$0	$0	$0
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	$0	$0	$0	$0
Total	All Sections	$1,859,510	$1,792,489	$2,057,241	$2,010,480

a. Over 10 years at 7 percent interest
b. Over 10 years at 3 percent interest

TABLE 9. AGGREGATE COMPLIANCE COSTS FOR HEMATOPOIETIC STEM/PROGENITOR CELL ESTABLISHMENTS

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs [a]	Total Annualized Costs [b]
1271.150	CGTP Requirements	$0	$0	$0	$0
1271.155	Exemptions & Alternatives	$0	$0	$0	$0
1271.160	Quality Program	$208,354	$457,200	$486,865	$481,625

TABLE 9. AGGREGATE COMPLIANCE COSTS FOR HEMATOPOIETIC STEM/PROGENITOR CELL ESTABLISHMENTS

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs [a]	Total Annualized Costs [b]
1271.170	Personnel	$739,100	$117,610	$222,841	$204,255
1271.180	Procedures	$0	$433,200	$433,200	$433,200
1271.190	Facilities	$90,784	$665,000	$677,926	$675,643
1271.195	Environmental Control & Monitoring	$90,784	$205,458	$218,383	$216,100
1271.200	Equipment	$450,621	$465,548	$529,706	$518,374
1271.210	Supplies & Reagents	$135,185	$8,265	$27,512	$24,113
1271.215	Recovery	$0	$0	$0	$0
1271.220	Processing and Process Controls	$198,550	$0	$28,269	$23,276
1271.225	Process Changes	$36,100	$119,130	$124,270	$123,362
1271.230	Process Validation	$678,775	$297,825	$394,467	$372,398
1271.250	Labeling Controls	$5,225	$0	$744	$613
1271.260	Storage	$0	$0	$0	$0
1271.265	Receipt, Predistribution Shipment & Distribution	$482,861	$28,080	$96,829	$84,686
1271.270	Records	$178,956	$2,880	$28,359	$23,859
1271.290	Tracking	$415,150	$164,160	$223,268	$212,828
1271.320	Complaint File	$90,784	$158,840	$171,766	$169,483
1271.350	Reporting	$0	$167,200	$167,200	$167,200
1271.370	Labeling	$0	$0	$0	$0
1271.400	Inspections	$0	$211,200	$211,200	$211,200
1271.420	HCT/Ps Offered for Import	$0	$0	$0	$0
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	$0	$0	$0	$0
Total	All Sections	$3,801,230	$3,501,595	$4,042,805	$3,947,215

[1] Over 10 years at 7 percent interest.
[2] Over 10 years at 3 percent interest.

TABLE 10.--AGGREGATE COMPLIANCE COSTS FOR ART ESTABLISHMENTS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs [1]	Total Annualized Costs [2]
1271.400	Inspections	$0	$307,200	$307,200	$307,200
Total	All Sections	$0	$307,200	$307,200	$307,200

[1] Over 10 years at 7 percent interest.
[2] Over 10 years at 3 percent interest.

TABLE 11.--AGGREGATE COMPLIANCE COSTS FOR SEMEN BANKS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs [1]	Total Annualized Costs [2]
1271.400	Inspections	$0	$84,480	$84,480	$84,480
Total	All Sections	$0	$84,480	$84,480	$84,480

[1] Over 10 years at 7 percent interest.
[2] Over 10 years at 3 percent interest.

TABLE 12.--AGGREGATE COMPLIANCE COSTS FOR ALL HCT/P INDUSTRY SECTORS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs [1]	Total Annualized Costs [2]
1271.150	CGTP Requirements	$0	$0	$0	$0
1271.155	Exemptions & Alternatives	$0	$0	$0	$0
1271.160	Quality Program	$495,351	$1,239,477	$1,310,003	$1,297,547
1271.170	Personnel	$1,333,181	$219,054	$408,869	$375,343
1271.180	Procedures	$0	$842,506	$842,506	$842,506
1271.190	Facilities	$107,950	$665,000	$680,370	$677,655
1271.195	Environmental Control & Monitoring	$105,622	$242,432	$257,470	$254,814
1271.200	Equipment	$587,933	$705,206	$788,914	$774,130
1271.210	Supplies & Reagents	$181,473	$38,539	$64,377	$59,813
1271.215	Recovery	$0	$0	$0	$0
1271.220	Processing and Process Controls	$267,440	$0	$38,077	$31,352
1271.225	Process Changes	$173,881	$265,118	$289,875	$285,503
1271.230	Process Validation	$1,526,255	$674,120	$891,424	$853,044
1271.250	Labeling Controls	$12,231	$0	$1,741	$1,434
1271.260	Storage	$0	$0	$0	$0
1271.265	Receipt, Predistribution Shipment & Distribution	$538,732	$448,128	$524,831	$511,284
1271.270	Records	$946,524	$3,688	$138,452	$114,649
1271.290	Tracking	$508,976	$337,098	$409,565	$396,766
1271.320	Complaint File	$122,235	$264,626	$282,029	$278,956
1271.350	Reporting	$0	$349,600	$349,600	$349,600
1271.370	Labeling	$0	$0	$0	$0
1271.400	Inspections	$0	$833,280	$833,280	$833,280
1271.420	HCT/Ps Offered for Import	$0	$0	$0	$0
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	$0	$0	$0	$0
Total	All Sections	$6,907,784	$7,127,872	$8,111,384	$7,937,674

[1] Over 10 years at 7 percent interest.
[2] Over 10 years at 3 percent interest.

As shown in table 7 of this document, the total one-time costs for the eye banking industry are estimated to be $1.25 million, and annual costs are estimated at $1.44 million. These figures generate a total annualized cost estimate of $1.59 million to $1.62 million. For the conventional tissue industry (table 8 of this document), aggregate one-time costs and annual costs are estimated at $1.86 million and $1.79 million, respectively. These figures correspond to an estimated

annualized cost of $2.01 million to $2.06 million. The hematopoietic stem/progenitor cell industry (table 9 of this document) is estimated to incur a one-time cost of $3.8 million and annual costs of $3.5 million, yielding an annualized cost estimate of $3.95 million to $4.04 million. ART establishments and semen banks are expected to incur no one-time costs under the CGTP final rule because they are subject only to the inspection and enforcement provisions as they relate to donor eligibility requirements under subpart C. The total annual and annualized costs for ART establishments and semen banks are estimated to be $0.31 million and $0.08 million, respectively. These cost estimates are presented in tables 10 and 11 of this document.

Table 12 of this document summarizes the total estimated cost impacts for all HCT/P industry sectors. FDA estimates the aggregate one-time compliance costs of the CGTP final rule to be $6.9 million. Annual costs, aggregated across all sectors of the HCT/P industry, are estimated to be $7.13 million. These estimates correspond to a total annualized cost estimate of $7.94 million to $8.1 million for the CGTP final rule applied to all major sectors of the HCT/P industry.

C. Estimated Benefits of the CGTP Final Rule

The purpose of the CGTP final rule is to prevent the introduction, transmission, or spread of communicable disease

through the use of HCT/Ps. Although voluntary industry standards exist for most of the affected products, FDA finds that public safety cannot be assured or effectively protected through reliance on these informal mechanisms. The existing industry standards also vary to some extent in their comprehensiveness, and there are variations in the extent to which firms in the affected industry sectors follow these voluntary standards.

For example, most industry consultants providing input for this analysis agreed that quality standards, such as those in the CGTP final rule, and similar standards recommended by industry, could substantially reduce the risk of HCT/P product contamination by communicable disease agents. However, most of these experts also agreed that, because additional costs are associated with maintaining higher quality standards, and because there is no explicit patient demand for higher quality standards to prevent contamination risks, some establishments are not currently following adequate quality control procedures. A regulatory requirement for quality systems and recordkeeping would provide the incentives needed to bring marginal establishments to a more uniform and appropriately high standard of quality in HCT/P processing.

The primary beneficiaries of the CGTP final rule are the patients who receive HCT/Ps. Benefits to patients result from

improved outcomes due to reduced risks of communicable disease transmission. Society as a whole will benefit from implementation of CGTPs due to improved safety of the supply of HCT/Ps, and reductions in health care and other costs associated with treating the complications arising from the use of contaminated tissue products. The discussion that follows considers some of the potential benefits of CGTPs based on a survey of the clinical literature.

Recent clinical literature indicates that each type of HCT/P affected by the CGTP final rule has documented communicable disease transmission risk that may be the result of contamination or other problems resulting from processing, or other steps in manufacturing. Although the limited number of adverse events reported in the clinical literature suggests a relatively low risk of communicable disease transmission associated with HCT/Ps, it is important to note that this evidence is generally based on analysis of a limited number of voluntarily reported incidents. The reported HCT/P problems provide a basis for assessing the magnitude of the potential benefit from further reducing the incidence of events that contribute to or increase the risk of communicable disease transmission. In some cases involving eye tissue, conventional tissue, or hematopoietic stem/progenitor cell products, HCT/P problems have required medical intervention to treat infection,

or to replace an implanted HCT/P. In some clinical applications, HCT/P related problems have increased the risk of patient morbidity or mortality. In general, FDA anticipates that the risk of communicable disease transmission will decline, and patient outcomes will improve, as a result of industry compliance with the provisions of the CGTP final rule.

The sections that follow describe specific product-related problems associated with communicable disease transmission that are at least partly attributable to a lack of uniform and enforceable standards in HCT/P manufacturing. The costs of correcting these problems are considered, to gauge the potential magnitude of the benefits associated with improvements in manufacturing processes brought about through implementation of CGTPs. The discussion is organized by type of HCT/P.

1. Eye Tissue

Primary corneal graft failure is a key adverse outcome of concern following corneal tissue transplant. Such failures result in additional graft attempts, and each attempt increases the risk of communicable disease transmission by exposing the recipient to another HCT/P, and another surgical procedure. Although primary corneal graft failure is relatively uncommon, its occurrence has been attributed to several factors related to tissue collection, processing, and product distribution. These factors include donor characteristics such as age (Ref. 5),

donor infectivity (e.g., with Herpes Simplex Virus and CJD) (Refs. 8 and 31), length of product storage, type of storage medium, and shipping distance from the eye bank to the recipient site. In an analysis of factors contributing to primary corneal graft failure, Wilhelmus et al. (Ref. 5) found that "the duration of donor corneal preservation may have a significant effect on endothelial vitality," citing studies that demonstrate endothelial cell loss in chondroitin-supplemented storage media after 7 to 10 days of storage. The authors suggest that, even with modern eye bank screening and preservation procedures, a donor corneal storage time greater than 1 week increases the risk of primary corneal graft failure by more than two-fold.

Wilhelmus et al. include in their analysis a summary of selected findings of studies published between 1971 and 1994 that report the incidence of primary graft failure for corneal transplants using 4 degrees Celsius preservation, and a variety of preservation methods. The rates of primary graft failure reported ranged from 0.9 percent to 3.1 percent, and a combined rate of 2.1 percent was estimated across all preservation methods. In their analysis of factors associated with corneal graft failures reported to the EBAA for 1991 to 1993, the findings of Wilhelmus et al. illustrate the importance of verification of quality and documentation of the receipt of supplies and reagents used in HCT/P processing. The authors

found that 86 cases (approximately 59 percent of all cases studied) of primary corneal graft failure shared preservation media from the same lots. These findings underline the importance of the CGTP requirement for verification of quality and documentation of receipt for each particular lot of processing media used in the manufacture of uniquely labeled and traceable products.

Primary corneal graft failure typically requires repeat surgery to replace the failed graft. The Agency for Healthcare Research and Quality (AHRQ), reports 598 total discharges for Principal Procedure 13, Corneal transplant, with a mean hospital length of stay (LOS) of 3.5 days and a mean hospital charge of $14,233 in 2000 (Ref.7). The estimated rate of primary graft failure, which may result from one or more aspects of cornea collection, processing, or distribution, ranges from 0.1 percent (based on the number of cases voluntarily reported to EBAA for the period 1991-1993, and again in 2001) to as much as 2.1 percent (combined failure rate reported in the literature, across the range of preservation media currently used in eye tissue processing, cited in Wilhelmus et al.). Based on 45,897 corneal transplants reported by the EBAA in 1999, the estimated number of cases of primary graft failure may range from 46 cases [0.001 x 45,897] to 413 cases [0.009 x 45,897] per year. The lowest estimate of the incidence of primary corneal graft

failure reported by Wilhelmus et al. (0.9 percent) was used in this calculation to produce a conservative estimate of the number of cases, and in response to public comments on the proposed CGTP rule. The total cost of replacement of a failed corneal graft is estimated to include $654 of physician services (Ref.8), including an office visit to diagnose the graft failure before hospitalization, and initial and followup physician visits during patient hospitalization for the repeated corneal transplant. It also includes one followup physician office visit to assess the outcome of the second transplant. The patient is estimated to further incur at least 1 week of time lost from work for doctor visits, hospitalization, and recovery of visual function after surgery. The cost of this patient time loss is estimated at $957.20, based on a 40-hour work week and U.S. average employer costs for employee compensation of $23.93 (Ref. 32). Thus, the current annual cost impact of primary corneal graft failure may range from $728,833 (46 x ($14,233 + $654 + $957.20)) to $6,543,655 (413 x ($14,233 + $654 + $957.20)).

The risk, incidence, and cost of treating primary corneal graft failure will be reduced through the implementation of CGTPs, due to provisions requiring the validation of processing methods and process quality controls, the verification of supplies and reagents, and improved documentation. The total

annualized cost to eye banks of implementing the CGTP final rule is estimated to be $1.61 million to $1.65 million, and the total cost of repeat surgery, hospitalization, physician's services and work loss associated with primary corneal graft failure is estimated to be $15,844.20 per occurrence ($14,233 + $654 + $957.20). Based on these estimates, if implementation of the CGTP final rule were to result in approximately 104 fewer cases ($1.65 million / $15,844 per case) of primary corneal graft failure per year, the benefits realized (in the form of avoided health care costs and income loss due to time away from work) would exceed the total annualized cost to eye banks, thereby making the rule cost effective for this sector of the HCT/P industry.

A reduction of 104 cases represents a 25 percent reduction (104 fewer cases / 413 total cases) in the risk of corneal graft failure (from 0.9 percent to 0.675 percent) based on the lowest rate reported by Wilhelmus et al. Due to uncertainty with respect to the actual risk of primary corneal graft failure, and the degree to which CGTPs would reduce this already uncertain risk, FDA is not able to determine whether or not implementation of this final rule would generate this level of risk reduction. No attempt was made to estimate the benefits of any potential reduction in the risk of intraocular infection (another HCT/P-

related problem associated with eye tissue) resulting from implementation of CGTPs due to a lack of data.

2. Conventional Tissue

Conventional tissue refers to a wide range of HCT/Ps including pericardium, dura mater, heart valves, skin allograft, bone allograft, fascia, tendons, and ligaments. FDA's survey of the clinical literature indicates that bone, skin and heart valve allografts each present a different potential for communicable disease transmission risk and graft failure, and thus different levels of potential benefits from improved processing procedures and quality assurance steps in HCT/P manufacture. The discussion that follows considers these three distinct conventional tissue products and thus areas of potential benefit.

a. Bone allograft. An analysis of the incidence, nature, and treatment of infection associated with bone allograft by Lord et al. (Ref.9), demonstrates the importance of quality standards and process requirements to prevent tissue contamination. Of the 283 patients in their analysis who had received a massive allograft of bone, infection developed in 33 cases (11.7 percent). The final outcome for those 33 patients was poor compared to the 250 uninfected patients. About 82 percent (27 of the 33 patients) of the infected allografts were considered failures of treatment because amputation or resection

of the graft was required to control the infection. Potential sources of contamination cited in the study include donor infection or contamination introduced during processing (estimated to occur in as many as 7 percent of the infected grafts), highlighting the critical need for HCT/Ps that are free from contamination by communicable disease agents. Other factors cited include duration of the operation, loss of blood, injury to soft tissue, and skin sloughing during the operation.

The importance of process validation is also implied by Hardin (Ref.10) in a review of banked bone allograft processes. In describing methods for sterilization, Hardin identifies ethylene oxide as one of the chemicals used, but indicates that its effectiveness may nonetheless be questionable, because of reports of graft failures in which residues of ethylene oxide have been implicated, and some experimental evidence indicating toxicity of ethylene oxide in human tissues.

Based on an average rate of 0.057 for bone allograft failure due to contamination (based on an estimated allograft infection rate of 0.07 x an estimated 0.82 failure rate for infected bone allograft), and the conservative assumption that all graft failures would be treatable through repeat surgery to replace the bone allograft, the associated healthcare costs could be on the order of $60 million per year ($59,679,928 = 0.057 x 44,000 x ($22,497 + $1,133)). This figure is based on a

national level estimate of 44,000 bone allografts per year (Ref.11), and a mean hospital charge of $22,497 for Principle Procedure 142, Partial excision of bone (Ref. 28). Physician costs per hospitalization are estimated to be $1,133, based on submitted charges per person served in the Orthopedic Surgery Physician Specialty category (Ref. 8).

The reported average length of hospital stay for bone surgery is approximately 6.3 days (Ref. 28). The estimated cost of patient time lost assumes that repeat surgery would require at least 1 week of time away from work, at an estimated value of $957.20, based on a 40-hour work week and average hourly compensation of $23.93 (Ref.32). This yields an estimated total patient time cost of $2,400,658 (0.057 x 44,000 x $9357.20). Thus, the total annual cost of bone allograft failure due to contamination is estimated to be approximately $62 million ($62,080,586 = $59,679,928 + $2,400,658).

If bone allograft failures result in amputation, the direct and indirect costs would be significantly higher. For example, the direct cost per hospitalization for lower extremity amputation is estimated to be $30,820 based on AHRQ Healthcare Cost and Utilization Project (HCUP) data (Ref. 23). Moreover, permanent disability following amputation imposes extremely high costs on the patient, the patient's family, and on society as a whole. The AHRQ HCUP data also report 5,200 in-hospital deaths

and a 4.5 percent death rate associated with these amputation procedures.

FDA is uncertain about the extent to which the estimated cost impact will be reduced through implementation of the CGTP final rule for two reasons. First, many graft failures result from transplantation procedures and other factors not related to bone allograft manufacture, or from a combination of factors. Second, some establishments may have already developed new bone processing methods that may greatly reduce infection risk. If as much as 90 percent of the estimated risk is actually attributable to other factors, or has already been addressed through better manufacturing processes, the benefit from CGTPs applied to the remainder of bone tissue processes and establishments would be on the order of $6.2 million ($62,080,586 x 0.10) per year. The total annualized cost of the CGTP final rule for all conventional tissue banks is estimated to be $2.03 million to 2.07 million, and the estimated total cost of treatment for infected bone allograft, including hospitalization, physician's office visits and work loss is $24,587.20 per occurrence. If implementation of the CGTP final rule resulted approximately 84 fewer cases of infected bone allograft requiring repeat surgery ($2,073,547 / $24,587.2 = 84.3), the benefits of CGTPs would exceed the estimated total annualized costs for all conventional tissue banks. This

reduction in the number of cases of bone allograft infection corresponds to a 3.3 percent reduction (84.3 fewer cases / 2,525.6 potential cases) in risk based on the information used as the basis for this analysis.

b. Skin allograft. —Skin allografts represent another type of HCT/P that is critically dependent on processing and quality controls to prevent the manufacture, distribution and/or use of contaminated products. The clinical literature reports cases of cytomegalovirus (CMV) transmission due to skin donor infection (Ref.12), and HIV contamination from infected donor skin tissue and subsequent tissue processing (Ref.13). CMV infections are usually not life-threatening in healthy individuals, but present grave risks to the types of patients who typically require skin grafts. In general, patients who have suffered severe burns and require skin grafts are immunosuppressed as a result of their injuries and are therefore susceptible to potentially life-threatening CMV infections. These include pneumonitis, retinitis, gastroenteritis, hepatitis, and neurological complications (Ref. 12). Contamination of skin allograft can also significantly affect burn patient survival. Because the clinical literature does not provide summary estimates of the risk of contamination associated with skin allograft, the agency is unable to quantify the level of associated risk. Although implementation of the CGTP final rule is expected to reduce the

risk of contaminated skin allograft, and thereby improve burn patient outcomes, FDA could not quantify this source of expected patient benefits due to a lack of necessary information.

c. Heart Valve Allografts. --Heart valve allografts, another of the many types of conventional tissue products, provides another compelling case for HCT/P production process validation and quality control. Human heart valve contaminants not effectively removed in tissue processing have resulted in serious infections that, at a minimum, require valve replacement and may also result in patient death. Sources of contamination of a heart valve allograft include the donor, the environment during harvesting and processing, and the operating room during implantation. Microbial contamination of human heart valves is common at tissue harvesting, with reports of over 50 percent contamination among valves retrieved in open mortuary areas. According to a study by Kuehnert et al. (Ref.14) common contaminants found before disinfection consist of gastrointestinal and skin flora (including coliforms), viridans group streptococci, Staphylococcus aureus, S. epidermidis, and Bacillus species. In general, bacterial contamination can be effectively removed through standard disinfection procedures used in most accredited conventional tissue banks. However, tissue that remains contaminated with these pathogens, particularly Staphylococcus and Streptococcus species, can cause

early onset allograft valve endocarditis. In contrast to bacterial contamination, reported rates of fungal contamination of heart valve allograft are relatively low. However, Kuehnert et al. report that rates vary widely (1.7 percent to 28.0 percent), and that the inclusion of anti-fungal drugs in tissue disinfection regimens is not effective in eradicating fungal contamination.

Fungal endocarditis is a rare but potentially fatal complication of allograft heart valve replacement. According to Kuehnert et al., the incidence of fungal endocarditis following surgery for heart valve replacement with allograft is estimated to range from 0.3 percent to 1.4 percent (midpoint estimate of 0.85 percent). In one reported case, the infected patient needed subsequent surgery to replace the valve and required treatment with intravenous amphotericin B for the following 8 weeks. In many cases, treatment is not successful and death results. In one review, cited by Kuehnert et al., over 40 percent of patients who had acquired fungal endocarditis after heart valve allograft implantation died within 2 weeks of diagnosis.

In their study, Kuehnert et al. describe the process controls used by AATB-affiliated establishments including the establishment, validation and documentation of decontamination protocols. Because these regimens have not been found effective

against fungal contamination, AATB-affiliated establishments routinely discard tissue with documented fungal contamination. However, according to Kuehnert et al., the supplier of over 85 percent of all heart valve allografts (approximately 41,000 since 1984) does not follow AATB standards, but instead follows a decontamination protocol that is reported to be proprietary. This protocol apparently includes efforts to disinfect rather than discard tissue with fungal contamination. However, efforts to eradicate fungal contamination identified in processing can be unsuccessful, and in this case, a false-negative culture following processing results in tissue being distributed for use in patients.

The CGTP final rule requires that all establishments use validated procedures and that HCT/Ps meet all release criteria before they are made available for distribution. Based on the rates of infection and mortality risk reported by Kuehnert et al., and an estimated 5,000 to 6,000 human heart valve allografts per year (these figures were reported to the agency by the largest supplier of this type of HCT/P in their comment on the proposed rule), there may be an estimated 43 (0.0085 x 5,000) to 51 (0.0085 x 6,000) cases of fungal endocarditis each year. These cases of fungal endocarditis may further cause an estimated 17 (0.0085 x 0.40 x 5000) to 20 patient deaths per year (0.0085 x 0.40 x 6,000). Fungal endocarditis may result

from a variety of peri- or post-operative factors including infection of the valve allograft itself. While highly uncertain, one comment suggested that as many as one-third of all cases of fungal endocarditis may be caused by contaminated valve allografts. Based on this information, FDA expects that there may be as many as 14 to 17 cases of heart valve contamination causing fungal endocarditis along with 5 to 7 patient deaths each year. Changes in processing procedures based on the CGTP requirements will help to avoid cases of fungal endocarditis and, perhaps, some of the resulting deaths. Substantial health care cost savings will also be achieved through improved processing controls and avoided adverse events due to implementation of the CGTP final rule.

AHRQ reports 82,874 total hospital discharges for Principle Procedure 43, Heart Valve Procedures in 2000 with a mean LOS of 11.1 days and mean hospital charges of $78,494 (Ref. 24). The AHRQ also reports 4,986 in-hospital deaths (and a 6.0 percent death rate) associated with these procedures. If patients undergoing this procedure were to lose 2 weeks of time away from work, the value of this work loss, based on a 40-hour work week and an average hourly compensation of $ 23.93 (Ref. 32), would be $1,914 per case. Based on reported average charges of $78,494 per hospitalization for implantation of a heart valve allograft (Ref. 24), estimated physician charges of $6,796 per

case, including repeat surgery and patient care during the average 11.1-day hospital stay, and 2 weeks of patient work loss, the total cost of treating cases of heart valve contamination causing fungal endocarditis would be between $1,220,862 (14 x ($78,494 + $6,796 + $1,914.4)) and $1,482,475 (17 x ($78,494 + $6,796 + $1,914.4)). These estimates should be viewed as conservative because they reflect only the costs associated with contaminated heart valve allografts causing fungal endocarditis, and do not consider the costs associated with the more common bacteria-induced early onset allograft valve endocarditis. No estimate of the potential benefit of CGTPs in reducing the cost of treating early onset allograft valve endocarditis was generated due to a lack of necessary information.

The total annualized costs of the CGTP final rule for conventional tissue banks are estimated to be $2.03 million to $2.07 million. The total costs associated with infected bone allografts and contaminated heart valve allografts causing fungal endocarditis are estimated to be between $61.3 million ($60.1 million + $1.2 million) and $61.6 million ($60.1 million + $1.5 million). If implementation of the CGTP final rule were to reduce these estimated costs by 3.3 percent, the estimated annual cost savings, or benefit, would exceed the estimated compliance costs. Thus, a 3.3 percent reduction in the cost

associated with only two HCT/P-related problems would make the CGTP final rule cost effective for the conventional tissue industry.

3. Hematopoietic Stem/Progenitor Cells

Promising outcomes from use of peripheral blood stem/progenitor cells (PBSC) and cord blood-derived stem/progenitor cells (CBSC) in lieu of bone marrow have resulted in increased collection and use of these products in hematopoietic stem/progenitor cell transplants. For example, recent studies have reported the use of PBSC (rather than bone marrow) in 54 percent (Ref. 15) and 62 percent of cases, respectively (Ref. 16). However, studies of hematopoietic stem/progenitor cell products indicate that products manufactured by this industry may become contaminated during collection and processing. Moreover, the therapy-induced immunosuppression of the oncology patients who receive these products places them at particularly high risk for serious infection and subsequent mortality. Manufacturing methods conforming to CGTP are necessary to prevent this threat to the safety and effectiveness of hematopoietic stem/progenitor cell therapies. For example, investigations of PBSC have reported that the large quantity of blood that must be processed to obtain adequate numbers of hematopoietic stem/progenitor cells resulted in large volumes of cryopreserved cells received by

patients. This process posed the risk of increased toxicity, because of the amount of dimethyl sulfoxide used for cryopreservation (Ref. 20).

Another quality concern with PBSC involves the maintenance of the sterile integrity of the apheresis catheter and component throughout the period of leukapheresis, cryopreservation, thawing, and transfusion (Espinosa et al., 1996) (Ref. 17). Webb et al. (Ref. 18) reported a 2.41 percent rate of bacterial contamination in PBSC products, and a 13.7 percent rate of infection of patients receiving contaminated products.

Although bacteremia-induced fever and other clinical sequelae are generally considered reversible, infections present more serious risks for hematopoietic stem/progenitor cell recipients than for the overall population. Survival rates for hematopoietic stem/progenitor cell transplantation are significantly reduced for patients who become critically ill. In a study of survival rates among hematopoietic stem/progenitor cell recipients admitted to an intensive care unit, Price et al. (Ref. 16) found that patients with probable infection had a significantly higher death rate (57 percent) compared to patients with no probable infection (13 percent). Multiple regression analyses by Price et al., controlling for other risk factors such as patient intubation, type of transplant, source of hematopoietic stem/progenitor cells, human leukocyte antigen

compatibility, type of malignancy and patient age, also found infection to be a significant predictor of mortality.

Based on reported blood collection and transfusion statistics (Ref. 25), a total of 32,291 units of PBSCs were collected, and 18,123 units transfused, in the United States in 1997 (the use of PBSCs has been increasing steadily since that time). Thus, an estimated 60 patients per year (18,123 PBSC transfusions x 0.024 x 0.137) could suffer infection following receipt of contaminated PBSC, based on the reported rates of 2.4 percent of patients receiving contaminated PBSC, 13.7 percent of those patients subsequently developing infection (Ref. 15), and 18,123 hematopoietic stem/progenitor cell transplants performed in 1997. Costs of treating patients who become infected after receiving contaminated hematopoietic stem/progenitor cell products are estimated based on 8,985 AHRQ-reported total discharges for Principle Procedure 3, Bacterial Infection, Unspecified Site, with average hospital charges of $21,221 per 6.9-day patient stay (Ref. 26). Estimated total health care costs also include physician costs of $918 assuming one initial in-hospital visit, and daily followup visits during the patient stay (Ref. 8). Patient income loss is valued at $1,914 based on estimated hourly compensation of $23.93 (Ref. 32) and an estimated 2 weeks away from work. Thus, the total annual cost impact of infection following transplant of contaminated PBSC

products is estimated to be $1,443,180 (60 x ($21,221 + $918 + $1,914)).

In addition to health care and time away from work costs, reducing the risk of contaminated PBSC products could result in avoiding 26 excess hematopoietic stem/progenitor cell patient deaths per year, due to infection. This number reflects the excess mortality risk reported for hematopoietic stem/progenitor cell recipients with infection versus those without infection. It is based on the following: (18,123 transplant procedures per year) x (2.41 percent PBSC patients receiving contaminated product) x (13.7 percent patients receiving contaminated product develop infection) x (44 percent excess mortality risk for hematopoietic stem/progenitor cell recipients with a probable infection). This estimate suggests a risk of death due to infection resulting from a contaminated hematopoietic stem/progenitor cell transplant of approximately 0.14 percent (26 deaths / 18,123 hematopoietic stem/progenitor cell transplants). FDA currently has no basis for predicting how many of these deaths might be avoided through implementation of the CGTP final rule.

As bacterial contamination has also been documented in studies of cord blood processing, the CGTP requirements for staff training and process validation will likely support risk and cost reduction efforts across the 25 CBSC establishments.

For example, a study by Kogler et al. (Ref. 18) found that, during the initial 6 months of a CB collection program, the median bacterial contamination rate was 18 percent. After extensive training in sterile procedures for the staff who collect cord blood, the contamination rate was reduced to 1 percent. Due to a lack of data regarding the incidence and risks associated with CBSC procedures, FDA currently has no basis for predicting the magnitude of benefits that might be realized from implementation of the CGTP final rule in this HCT/P industry sector.

D. Summary of cGTP Benefits

This analysis of the potential benefits of the CGTP final rule has considered its impact on major sectors of the HCT/P industry by focusing on problems associated with HCT/Ps cited in the literature, and the costs of correcting those problems. This review suggests that current industry voluntary standards are not followed uniformly, and that implementation of the CGTP final rule has the potential to generate economic benefits by reducing communicable disease transmission risks, improving product safety, and by reducing the costs associated with correcting HCT/P related problems.

Table 13 of this document provides a summary of the particular products, problems identified and their associated costs based on the agency's survey of the literature. FDA

estimated the associated health care costs based on reported risks, national level database estimates of the numbers of patients undergoing related procedures, and estimates of the direct medical costs associated with those procedures. These estimates also reflect the cost of work loss experienced by patients undergoing treatment to correct HCT/P related problems.

Rather than attempting to generate point estimates of the benefits of the CGTP rule, the agency has chosen to present the results of this analysis of potential benefits in cost-effectiveness or break-even terms. There are several reasons for this. First, the current or baseline risks associated with the various types of HCT/Ps are unknown because the data required to establish these risks is either not readily available or is not currently collected by any entity. The lack of comprehensive risk data for the HCT/P industry is due primarily to a lack of mandatory reporting requirements for adverse health events associated with human tissues, a situation that is addressed by the reporting requirements of the CGTP final rule. Second, given that the current baseline risks associated with various types of HCT/Ps are uncertain, FDA has no basis for determining defensible estimates of the degree to which implementation of the CGTP final rule might be expected to reduce these already uncertain risks. Finally, while limited data with which to characterize a few of the risks associated with a select few of

the many and diverse HCT/Ps, it is not possible to fully characterize all of the potential problems associated with all of the HCT/Ps that would be affected by this rule. Thus, it is not possible to develop comprehensive estimates of the aggregate benefits of the CGTP final rule.

TABLE 13.--SUMMARY OF CGTP BENEFITS

HCT/P Industry Sector	HCT/P-Related Problem	Avoided Treatment Outcome	Estimated Cost of Treatment	Cost-Effective Percent Reduction in Cost/Risk
Eye Tissue	Primary Corneal Graft Failure	Repeat Surgery	$.729 to $6.5 million $15,844 per case	25%
Conventional Tissue	Bone Allograft Infection/Graft Failure	Repeat Surgery/Amputation	$62 million $24,587 per case	3.2%
Conventional Tissue	Heart Valve Fungal Endocarditis	Repeat Surgery (Death)	$1.2 to $1.5 million $87,204 per case	3.3%
Hematopoietic Stem/Progenitor Cells	PBSC Transplant Infection	Hospitalization (Death)	$1.4 million $24,053 per case 26 deaths	Unable to Determine

Additional uncertainties associated with estimating the benefits of the CGTP final rule include: The actual extent of current compliance in each of the affected industry sectors, the direct impact of HCT/P related problems on patient outcomes, and the precise size of the affected patient populations. Because of the limits of available data, the forgoing analysis has focused on a limited set of HCT/Ps. It is not certain how well these data represent the most critical areas, or actual levels of risk, associated with the many and varied products produced by the HCT/P industry. For some products, such as demineralized bone, the industry has achieved important advances in processing

that have improved the safety and effectiveness of products. Thus, the analysis of benefits based on problem reports from several years ago, may overstate the potential for improvements in the current industry practice. In other cases, the publication of the recent reports suggests that deficiencies still exist within current practices. These areas present important opportunities to avoid product failures due to HCT/P-related problems, which lead to unnecessary communicable disease transmission risks and greater health care costs.

E. Small Entity Impacts

The Regulatory Flexibility Act requires agencies to assess whether a rule may have a significant economic impact on a substantial number of small entities. Based on size standards established by the SBA, a small establishment in this industry sector (NAICS code 621991, Blood and Organ Banks) has annual receipts of less than $8.5 million (Refs. 21 and 22). In every sector of the HCT/P industry, the majority of establishments are estimated to be classified as small entities. However, because of the large number of entities currently following industry voluntary standards, the increase in costs is expected to be limited primarily to establishments that do not follow those existing standards. To assess the impact of the CGTP rule on small businesses, FDA first calculated the ratio of average compliance costs to average annual revenues, assuming that all

establishments will incur similar costs. The small entity impacts estimated below also focus on establishments that will be newly compliant under the CGTP final rule, and thus will experience the greatest potential new cost burden. Although current quality management practices at nonaccredited establishments may vary, and not every facility will incur every new cost estimated in table 4 of this document, the analysis that follows also considers a worst-case scenario in which every estimated cost is incurred by an establishment, to provide additional insight as to the maximum potential impact on small entities. While some firms may have lower than estimated average revenues, making them potentially more sensitive to cost increases, FDA does not know the distribution of firms by revenues because this information is not readily available. Therefore, the agency requested detailed industry comment regarding our average annual revenue assumptions in the CGTP proposed rule. To the extent possible, information obtained during the comment period has been incorporated into this analysis of the small entity impacts of the CGTP final rule. The results of this analysis are summarized in table 14 of this document.

A 1995 study of conventional tissue banks (Ref. 19) reports average annual revenues of $1.23 million per establishment, which translates into $1.45 million per establishment (in the

year 2002 dollars) based on inflation data reported by the Bureau of Labor Statistics (Ref. 27). Most eye banks, conventional tissue banks and hematopoietic stem/progenitor cell establishments were assumed to have a comparable level of average revenues in the proposed rule, and that assumption is retained here.

Within the eye banking industry, experts estimate that virtually all of the 134 establishments would be classified as small, and all are believed to follow the current industry (EBAA) standards. The average annual revenue per eye bank is estimated at $1.45 million. If an eye bank were to incur every new cost estimated for establishments in that industry sector, the total cost impact, including total one-time and annual costs, would be $39,750, which represents 2.7 percent ($39,750 / $1.45 million) of estimated annual revenues. Average annualized compliance costs are estimated to be $12,087 ($1,619,659 total annualized costs / 134 small eye banks), and represents 0.83 percent ($12,087 / $1.45 million) of average annual revenues per firm.

In the conventional tissue banking industry, an estimated 75 to 80 percent of the total of 166 establishments may be classified as small entities. Industry experts also estimate that 75 to 80 percent of those establishments currently follow AATB standards, which generally meet or exceed the requirements

of the CGTP final rule. Based on the assumed levels of increased effort and costs shown in table 4 of this document, the remaining 20 to 25 percent of small establishments that do not follow current AATB standards could incur up to $66,621 in total incremental costs, including both one-time and annual costs, assuming that every potential area of new quality management effort will be needed under the worst-case scenario. The average annual revenue per small conventional tissue bank is estimated at $1.45 million. Thus, the estimated maximum potential new costs would represent approximately 4.6 percent ($66,621 / $1.45 million) of this average annual revenue figure. The average total annualized cost for a small conventional tissue bank is estimated to be $11,678 ($1,506,433 total annualized costs / 129 small conventional tissue banks), and represents 0.8 percent ($11,678 / $1.45 million) of average annual revenues.

The agency estimates that approximately 250 hematopoietic stem/progenitor cell establishments may be classified as small entities, and that these establishments have average annual revenues of $1.45 million. An estimated 200 (or 80 percent) of these small establishments follow the current FACT or AABB standards but will incur some additional costs. If one of these establishments were to incur new costs for each of the relevant provisions identified in table 4 of this document, the total

incremental cost per establishment, including total one-time and annual costs, would be approximately $21,602. This figure represents approximately 1.5 percent ($21,602 / $1.45 million) of estimated annual revenues. The estimated 50 (or 20 percent of) small hematopoietic stem/progenitor cell establishments that do not currently comply with AABB or FACT standards will incur greater costs, as shown in table 4 of this document. If one of these establishments were assumed to incur every new cost identified in the cost analysis, the total one-time and annual costs would be approximately $83,483. This represents approximately 5.8 percent ($83,483 / $1.45 million) of average annual revenues.

The average annualized costs incurred by small hematopoietic stem/progenitor cell establishments would also vary depending on current practices and the degree to which establishments follow AABB or FACT standards. If a small hematopoietic stem/progenitor cell establishment is currently following industry standards, the average annualized cost associated with the CGTP final rule is estimated to be $8,367 ($1,673,301 total annualized costs / 200 small hematopoietic stem/progenitor cell establishments), and represents approximately 0.58 percent ($8,367 / $1.45 million) of the average annual revenue of these firms. However, if a small establishment is not following the current industry standards, a